AN EVALUATION OF THE EFFECTS OF THE NATIONAL INSTITUTES OF HEALTH'S CLINICAL TRIAL POLICIES ON RESEARCH GRANT PERFORMANCE

by

Eugene Ignatius Kane III, MPH

A dissertation submitted to Johns Hopkins University in conformity with the requirements for the degree of Doctor of Public Health

Baltimore, Maryland
May 2020

Abstract

Background: The National Institutes of Health (NIH) has implemented numerous policies to enhance stewardship of clinical trial grants. These policies seek to improve identification, monitoring, oversight, completion, and results reporting of clinical trials. Some of these policies have been met with concern from the researcher community regarding negative consequences on research. To date, no systematic evaluations of the impact of these policies on research grant performance have been conducted. This dissertation characterized the NIH clinical trial policies and evaluated how the key policies impacted a trial's relative citation ratio and recruitment progress.

Methods: In Aim 1, I identified the new and revised NIH and National Institute of Mental Health (NIMH) clinical trial policies and summarized the potential benefits and potential burdens of those policies. In Aim 2, I conducted an observational, single-group, pre/post evaluation of the association between the NIMH recruitment monitoring policy and the Relative Citation Ratio for NIMH-funded clinical trial grants. In Aim 3, I conducted a quasi-experimental study examining the effect of the new NIH clinical trial definition policy on recruitment progress. Using a difference-in-differences design, this Aim compared recruitment progress before and after the policy took effect in a group of studies newly-identified as clinical trials under the policy relative to a comparison group of clinical trials unaffected by the new policy.

Results: In Aim 1, five new/revised NIH-wide and four NIMH-only clinical trial policies were identified. The potential benefits associated with these policies were the improved identification, review, conduct, and reporting of publicly-funded clinical trials. Concerns over lost time, funding, and productivity due to administrative requirements were consistently identified as potential burdens. In Aim 2, a positive association was found between the implementation of a recruitment monitoring policy and the mean

relative citation ratio for clinical trial grants. In Aim 3, the revised clinical trial definition policy had no effects on the recruitment progress in NIMH-funded grants at 20 months.

Conclusions: Further research is needed to affirm these results with larger and more representative samples. Improved stakeholder engagement and planned policy outcome evaluation are recommended in future NIH and NIMH policy development.

Advisor:

Beth McGinty, PhD, MS

Readers:

Gail Daumit, MD, MHS

Brendan Saloner, PhD

Roberta Scherer, PhD, MS

Kevin Fain, DrPH, JD, MPH

Alternates:

Adam Spira, Ph.D.

Elizabeth Ann Skinner, M.S.W.

Acknowledgements

My time at the Johns Hopkins Bloomberg School of Public Health has been filled with wonderful interactions with phenomenal faculty and fellow students. I am immensely grateful to my advisor, Beth McGinty, whose adept guidance and positivity made this dissertation an exciting adventure. I appreciate the thoughtful critiques from my dissertation advisory committee which improved not only my research but also my professional skills. I am thankful for the continual support of my family—especially my wife Alejandra who was with me through every step of this journey. Finally, I would like to thank my past and present colleagues in the Office of Clinical Research, primarily Pamela Shell and Nitin Gogtay, for their support.

Table of Contents

List of Tables

Manuscript 1

Manuscript 2

Manuscript 3

List of Figures

Introduction

The National Institutes of Health (NIH) has developed and implemented numerous policies to enhance stewardship of clinical trial grants. These policies seek to improve identification, monitoring, oversight, completion, and results reporting of clinical trials. Some of these policies have been met with concern by the researcher community. To date, no systematic evaluations of the impact of these policies have taken place. This dissertation characterizes the NIH clinical trial policies and evaluates how key policies impact recruitment performance and relative citation ratios.

To accomplish this goal, Aim 1 compiles and characterizes all NIH clinical trial policies implemented from 2005-2019 to establish the NIH-wide clinical trial policy landscape. This characterization includes the policy goals, potential benefits, and potential burdens identified through public comments. The NIH-wide policies establish a common standard, but individual Institutes/Centers within the NIH can implement additional policy structure to suit the needs of their mission (layering the Institute-specific policies on top of the NIH-wide policies). With that in mind, this aim will also identify the scope of the Institute/Center-specific clinical trial policies of the National Institute of Mental Health (NIMH). The NIMH was an early adopter of several clinical trial policies which were subsequently adopted as NIH-wide policies, including a recruitment milestone and reporting policy examined in Aim 2.

From the range of NIH policies characterized in Aim 1, the impact of two specific policies are the focus of Aims 2 and 3. The first policy (Aim 2) is a recruitment milestone and reporting policy that requires clinical trials to establish timelines (milestones) for recruitment progress and update the NIH on that progress. The NIH-wide implementation of this recruitment milestone and reporting policy is too recent (fiscal year 2019) for adequate outcome data collection, but the NIMH has had a similar policy in place since the start of fiscal year 2006. The impact of the NIMH policy on the relative citation ratio, a grant performance outcome metric, can provide insight into the impact of the subsequent NIH policy.

The second policy (Aim 3) is a revision to the NIH definition of a "clinical trial." This policy was announced in 2014 and became effective for grant applications funded in fiscal year 2016. NIH uses this definition in other policies to determine the applicability of numerous administrative requirements (identified in Aim 1). Non-biomedical researchers have raised concerns that the revised definition, which expands the studies deemed clinical trials to include many studies testing social and basic behavioral interventions, imposes undue burden on research that is newly considered a clinical trial under the revised policy. Therefore, the third aim of this dissertation examines the impact of the revised clinical trial definition on study progress for NIMH-funded clinical trials. NIMH clinical trials were chosen because the NIMH began internally recording and tracking which NIMH-funded grants met the revised NIH definition of a clinical trial in FY2015 before the definition officially went into effect in FY2016 (and before formal NIH-wide tracking began in FY2019). NIMH's early tracking affords an opportunity to evaluate this policy before NIH-wide data are available. The NIMH also funds many studies of the basic behavioral and social science interventions that are now considered clinical trials.

Manuscript 1: Potential Benefits and Burdens of National Institutes of Health and National Institute of Mental Health Clinical Trial Policies

Abstract

Background: The National Institutes of Health (NIH) and the National Institute of Mental Health (NIMH) have implemented a suite of clinical trial policies in recent years. These policies have well-intended goals but concerns of undue burden have been raised by basic behavioral science researcher organizations. To date, no systematic characterization of these clinical trial policies has been performed.

Methods: This study identified the new and revised NIH and NIMH clinical trial policies from 2005-2019 and summarized the potential benefits and potential burdens of those policies. The NIH and NIMH clinical trial policies were manually identified from the NIH Guide for Grants and Contracts. Potential benefits and potential burdens were identified from a manual review of the policy notices, news articles, journal articles, press releases, websites, and official correspondence returned in searches of Google News, the Association for Psychological Science, the Federation of Associations in Behavioral & Brain Sciences, the American Psychiatric Association, and the American Psychological Association.

Results: Five new/revised NIH-wide and four NIMH-only clinical trial policies were identified from fiscal years 2005-2019. Potential benefits were the improved identification, review, conduct, and reporting of publicly-funded clinical trials. Potential burdens were loss of researcher time, potential loss of future research funding opportunities for basic behavioral researchers, and widespread confusion (for both researchers and the general public) resulting from an overlap between clinical trials and basic science.

Conclusions: Future clinical trial policy development would benefit from early engagement of researchers as stakeholders. The NIH and NIMH should publicly incorporate benefit/burden analyses and outcome evaluations into future policy development.

Introduction

The National Institutes of Health (NIH) is the largest biomedical research agency in the world (NIH, 2019d). Over 80%, or over $31 billion USD, of the annual NIH budget is awarded through competitive grants and contracts to external researchers across the U.S. and internationally (NIH, 2019c). As a federal funding agency, the NIH must assure good stewardship of public funds and rigorous science (G.A.O., 2016). This charge extends beyond the parent agency, the NIH, to the individual Institutes/Centers, such as the National Institute of Mental Health (NIMH), that issue awards in their relevant scientific mission.

The framework for oversight of funded research can be described through an adaptation of Donabedian's model for quality of care (Donabedian, 2005). The Donabedian model describes the flow of influence from an organization's structure to its processes and from the processes to the outcomes. Changing one element can have an impact on the downstream elements; therefore, outcomes can be influenced positively or negatively by processes and by structure. The NIH establishes a structure for research by requiring grantees to follow policies outlined in the terms and conditions of the grant award. The NIH-wide policies lay a structural foundation for all grants, while Institute/Center-specific policies, such as those of the NIMH, continue to build upon that foundation. Because grant funding is dependent upon compliance with this policy structure, the NIH and NIMH can use the policies to influence the downstream research process at grantee research institutions. Further downstream, the NIH can evaluate the effect on outcomes through research publications, results reporting in ClinicalTrials.gov, and potentially other metrics such as changes to clinical guidelines.

Despite this structure, the NIH has historically struggled to provide data to demonstrate full stewardship of clinical trials across the agency (G.A.O., 2016). In 2016, an evaluation by the Government Accountability Office (GAO) recommended that the NIH "(1) finalize data on clinical trial activity that the [Office of the NIH Director] needs to collect from Institute/Centers, and (2) establish and implement a

process for using those data (G.A.O., 2016)." In response, the NIH launched a comprehensive set of policy initiatives to "ensure rigor, transparency, and effectiveness of the US federally-funded clinical trial enterprise" beginning that same year and continuing through 2019 (Lauer & Wolinetz, 2016; NIH/OER, 2017b). Grantees have repeatedly expressed concern that the burden of compliance with these clinical trial policies will slow scientific progress (NIH, 2016a).

The goals of this study are to identify and summarize the scope, potential benefits, and potential burdens of both the NIH-wide and NIMH-specific clinical trial policies. The range of policies characterized in this study will establish the clinical trial policy landscape for NIMH-funded clinical trials.

Methods

Study Overview

This study systematically identified and summarized the potential benefits and burdens of NIH-wide and NIMH-specific clinical trial policies from Fiscal Year 2005-2019. Clinical trial policies were defined as any policy which set different or additional expectations or requirements for NIH-funded grants with clinical trials in human subjects as compared to grants with non-trials in human subjects. General human subjects research policies that apply to all research with humans are not clinical trial-specific policies and do not fall within the scope of this project. Potential benefits were defined as potential positive outcomes described as likely to result from a specific clinical trial policy. Potential benefits could be prospectively identified by the NIH/NIMH ("intended benefits") or subsequently by external stakeholders ("perceived benefits"). Potential burdens were defined as potential negative outcomes described as likely to result from a specific clinical trial policy. Potential burdens could be forecasted by the NIH/NIMH ("anticipated burdens") or by external stakeholders ("perceived burdens"). The fiscal year (FY) corresponds to the Federal Fiscal Year, which begins on October 1st of the previous

calendar year and ends on September 30th of the same year (e.g., FY2005 was October 1, 2004 through September 30, 2005).

Identification of Documents Describing Clinical Trial Policies, Potential Benefits, and Potential Burdens

Identifying Clinical Trial Policies

The NIH Grants Policy statement contains the full requirements of policies, terms, and conditions for accepting NIH funding to conduct research (NIH, 2018b). When new NIH or NIMH policies are announced, or existing policies are revised, this information is published in the NIH Guide for Grants and Contracts as a notice. Notices announced in the NIH Guide for Grants and Contracts supersede the Grants Policy Statement until the policy is incorporated into the next revised version of the Grants Policy Statement (NIH, 2018b).

The version of the NIH Grants Policy Statement in effect for FY2005 was reviewed to identify the existing clinical trial requirements at that time. Following the identification of clinical trial policies in effect in FY2005, the NIH Guide for Grants and Contracts was examined for NIH-wide and NIMH-specific clinical trial policy notices from FY2005-2019. Using the Guide's search function, the results were filtered for notices containing the word "trial." The returned results were reviewed by hand to determine whether the notice included a clinical trial policy, defined as text explicitly establishing an NIH/NIMH requirement that applies to a clinical trial grant application or award but does not apply to a non-trial application/award.

Identifying Potential Benefits and Potential Burdens

Potential benefits and potential burdens were identified from: the policy notice; NIH/NIMH public announcements; and searches of Google News, the Association for Psychological Science (APS),

the Federation of Associations in Behavioral & Brain Sciences (FABBS), the American Psychiatric Association, and the American Psychological Association. The search terms were the exact policy title and/or the policy announcement control number (see appendix). Google News was chosen to capture potential press releases and news coverage of policies and implications. The APS and FABBS were identified in formative research as the primary professional societies coordinating commentary on behalf of their members and other concerned professional organizations. The websites of the American Psychiatric Association and the American Psychological Association were also searched using the same methodology; however, these associations did not release independent press statements. Instead, they submitted their statements through FABBS (as co-signatories). Search results returned news articles, journal articles, press releases, webpages with relevant content, and official correspondence (i.e., publicly disclosed letters between NIH and aforementioned parties).

Data Abstraction

Abstraction Process

Potential benefits and potential burdens were identified from a manual review of the policy notices, news articles, journal articles, press releases, websites, and official correspondence returned in the search results. Formal NIH responses (i.e., direct correspondence in reply to letters sent by stakeholders to NIH) to concerns of burden were identified during data abstraction. In some cases, the NIH response was an alteration of the policy interpretation or implementation. Therefore, each NIH response was hand-reviewed to identify if the response changed the clinical trial policy (including a delay of the policy effective date).

Abstraction Tool

The data were collected in a Microsoft Excel spreadsheet for consolidation and analysis. Measures used to characterize the data were: type of notice, policy number (NIH Guide notice number), policy title, announcement date, effective date, effective fiscal year, policy summary, intended benefits (identified by NIH/NIMH), anticipated burdens (identified by NIH/NIMH), perceived benefits (identified by news and professional society searches), and perceived burdens (identified by news and professional society searches).

Data Analysis

Through this analysis, the policy intent and rationale were summarized from the policy notice for each NIH-wide clinical trial policy. The intended and perceived benefits, anticipated and perceived burdens, and subsequent NIH alterations were then identified and summarized for each policy. The NIMH-specific clinical trial policies were identified and summarized using the same methodology. The initial NIH-wide clinical trial requirements and the subsequent 2005-2019 NIH and NIMH clinical trial policies were collated chronologically by effective fiscal year to establish a timeline of changes and current policy requirements.

Limitations

The frequency of result “hits” could not be identified because many of the same burdens were either repeated or "co-issued" as joint statements between various groups. In some cases, 2 organizations would identify the same burden separately, or a single organization would publish the same burden concern numerous times in different formats. Because formal evaluations of the

magnitude of benefit/burden are not available, this summary was limited to focusing on published potential benefits and potential burdens rather than actual measured benefit/burden. Additionally, a summary of perceived burdens for the NIMH-specific policies was not possible because all returned results were NIMH-authored (i.e., no results from non-NIMH sources).

Results

The search of clinical trial policies returned 1620 NIH-wide and 761 NIMH-only notices published in the NIH Guide to Grants and Contracts from FY2005-2019. Of these, 90 NIH-wide notices and 168 NIMH-only notices contained the word "trial." After hand review of the notice summaries, 42 NIH-wide notices and 19 NIMH-only notices were determined to be directly related to clinical trials. This subset of notices was then reviewed further to determine whether each notice met inclusion criteria. In total, five new NIH-wide and another five new NIMH-specific clinical trial policies were identified. For the five NIH-wide clinical trial policies, the potential benefits identification process returned nine news articles and seven NIH postings while the potential burden identification returned nineteen news articles, three APS results, twelve FABBS results, and one NIH posting. The results also returned three NIH letters, six NIH-authored blog posts/articles, and one news article responding to perceived burdens.

Existing 2005 NIH Clinical Trial Policies

There were four clinical trial-specific policies that were in effect in 2005, the start of the study period (NIH, 2003). These existing policies are summarized in Table 1. The first policy defined the "clinical trial" term (see Table 2). The second policy defined Phase III clinical trials. The third policy mandated a formal data and safety monitoring plan (DSMP) for all clinical trials commensurate with the size and complexity of the trial. The DSMP is evaluated as part of the peer-review process. This policy

also identifies key factors for determining the frequency of monitoring, determining the person/persons responsible for conducting the monitoring, and the frequency and method of reporting safety events to other oversight entities. The fourth policy is the requirement for Data and Safety Monitoring Boards (DSMB) for multi-site clinical trials involving risks to participants and generally for phase III trials.

Table 1. NIH Clinical Trial Policies in Effect in 2005

Policy	**Policy Summary**
Clinical Trial Definition	Defined term "clinical trial" for NIH-funded research. See Table 2.
Phase III Clinical Trial Definition	Definition: "Clinical investigation (usually involving several hundred or more human subjects) to evaluate an experimental intervention in comparison with a standard or control intervention or to compare two or more existing treatments."
Data and Safety Monitoring Plans	NIH requires a formal data and safety monitoring plan to ensure the safety of participants and the validity and integrity of the data as part of the peer-reviewed funding application. The planned level of monitoring should be commensurate with the risks and the size and complexity of the clinical trial.
Data and Safety Monitoring Boards	NIH requires the establishment of DSMBs for multi-site clinical trials involving interventions that entail potential risk to the participants and generally for phase III clinical trials.

FY2005-2019 Clinical Trial Policies

Five new/revised NIH clinical trial policies put in place between fiscal year 2005 and fiscal year 2019 were identified. The first policy, entitled "Provision of Antiretroviral Treatment for Trial Participants Following their Completion of NIH-Funded HIV Antiretroviral Treatment Trials in Developing Countries," required investigators/contractors to address the provision of antiretroviral treatment to trial participants after their completion of the trial for antiretroviral treatment trials conducted in developing countries (NIH, 2005). While the notice itself was a guidance document, it did state that the NIH expected a plan to be included when considering funding decisions (making the plan a *de facto* requirement).

The second policy, entitled “Notice of Revised NIH Definition of ‘Clinical Trial,’” redefined which studies NIH considers a clinical trial (NIH, 2014b). Table 2 compares the old NIH definition, the revised NIH definition, the definition shared by both the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE), and the definition used by other US Government agencies in the federal Common Rule. As illustrated in table 2, the revised NIH definition is more consistent with other published definitions from prominent sources.

Table 2. Comparison of Clinical Trial Definitions

Organization	Clinical Trial Definition	Comparison to current NIH definition
NIH (pre-2014) (NIH, 2003)	A biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).	Pre-2014 definition is broad and does not link the effect of interventions to health-related outcomes. Examples provided in the policy are primarily biomedical.
NIH Current (post-2014) (NIH, 2014b)	A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.	Current NIH definition
WHO/ICMJE (ICMJE, n.d.-b; WHO, n.d.)	Any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and effect relationship between a health-related intervention and a health outcome.	WHO/ICMJE definition includes requirement that the intervention is health-related. WHO/ICMJE define health-related interventions as those used to modify a biomedical or health-related outcome. Consistent with NIH definition which uses the same criteria to define intervention (NIH/OER, 2017a).
Federal "Common Rule" (DHHS, 2017)	A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.	Equivalent to NIH definition (NIH/OER, 2017a).

The third new clinical trial policy, entitled "Policy of Funding Opportunity Announcements (FOA) for Clinical Trials," required that all applications involving one or more clinical trials be submitted through a Funding Opportunity Announcement (FOA) specifically designed for clinical trials (NIH, 2016b). This policy was announced in September 2016 and became effective for grants funded in fiscal year

2019 and later. With this new policy, the NIH would no longer accept NIH-defined clinical trial funding applications under announcements that are not specifically designed to accept clinical trials. In concert with these revised announcements, the grant application form was revised to more clearly identify clinical trial applications and describe key elements of the clinical trial design as well as identify recruitment and inclusion targets and milestones (NIH, 2017a). Further, applications submitted under these new clinical trial funding opportunity announcements would be evaluated using clinical trial-specific review criteria (NIH, 2017b).

The fourth new clinical trial policy, entitled "Policy on Good Clinical Practice Training for NIH Awardees Involved in NIH-funded Clinical Trials" was announced in September 2016 with an effective date of January 1, 2017 for any active and future NIH-funded clinical trials (NIH, 2016c). This policy established NIH's expectation for clinical trial awardees that clinical trial staff would be trained in Good Clinical Practice (GCP) consistent with the International Conference on Harmonisation.

The fifth new clinical trial policy, entitled "NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information" was announced in September 2016 with an original effective date of January 2017 (NIH, 2016a). This policy required that any NIH-funded clinical trial must register with and report results to ClinicalTrials.gov. This policy notice followed a request for public comment on the proposal (NIH, 2014a). The clinical trial policies, potential benefits, and potential burdens are summarized in Table 3.

Intended/Perceived Benefits

Numerous proposed benefits were attributed to these new clinical trial policies. The policy requirement to address post-trial antiretroviral therapy access was perceived by NIH and other

stakeholders to reduce the risk of subsequent treatment failure due to lapsed/interrupted treatment upon study completion (NIH, 2005; Shah, Elmer, & Grady, 2009).

NIH identified five intended benefits of the revised definition of "clinical trial." This policy was intended to (1) clarify the definition, (2) improve the identification and tracking of clinical trials, (3) enhance the NIH's review of clinical trial applications, and (4) ensure investigators are meeting their obligations related to conducting clinical trials and improve the oversight and transparency (i.e. results sharing) of clinical trials, (NIH, 2014b; NIH/OER, 2017b). The NIH also stated that the revised definition was intended to (5) help the NIH to fund mission-relevant, high-priority trials without needlessly duplicating previously conducted trials (Hudson, Lauer, & Collins, 2016). These NIH leaders noted that clinical trials frequently suffer from poor design and structure and many trials fail to publish results or submit data to a public database.

NIH identified three intended benefits of the clinical trial-specific funding opportunity announcement policy. In the policy announcement and companion article, NIH stated that this policy was intended to (1) improve NIH's ability to identify proposed clinical trials, (2) ensure that key pieces of trial-specific information are submitted with each application, and (3) uniformly apply trial-specific review criteria that focus on trial rationale, design, and analysis plans (Hudson et al., 2016; NIH, 2016b).

Three intended benefits of the GCP training policy were identified. The policy announcement proposed that the policy would (1) improve the safety of human research participants, (2) increase the scientific rigor, and (3) increase the reliability of study data (NIH, 2016c). NIH noted that GCP training provides a consistent and high-quality standard for conducting clinical trials (Hudson et al., 2016).

The ClinicalTrials.gov registration and results reporting policy received significant public support for both the proposal and its application to all NIH-funded clinical trials particularly since these trials are funded with public money (NIH, 2016a). Four potential benefits of the policy were identified. (1) NIH

proposed that the availability of results information will benefit investigators who will have access to more data, IRBs when evaluating risks and benefits, and the general public (NIH, 2016a). (2) NIH also proposed that the policy would reduce unintended duplication by providing more complete information for potential funders (Hudson et al., 2016). The ICMJE and various NIH authors proposed that the policy (3) fulfilled an ethical obligation to publicly share clinical trial data since participants placed themselves at potential risk to contribute to generalizable knowledge and (4) improved science by reducing publication bias and advancing the knowledge base of a field (ICMJE, n.d.-a; Taichman et al., 2016; Zarin, Tse, Williams, & Carr, 2016).

Anticipated/Perceived Burdens

As shown in Table 3, most potential burdens were perceived burdens identified by external stakeholders. Many of the perceived burdens were not identified as anticipated burdens by NIH in the policy notices or accompanying articles.

Two potential burdens of the antiretroviral treatment access planning policy were identified. First, the NIH acknowledged that its own authority to "encourage and support research" does not extend to supporting treatment provision following the completion of that research (NIH, 2005). Second, the policy may establish differential expectations for the provision of care to trial participants versus non-participants in those regions (Millum, 2011).

While the policy revising NIH's definition of clinical trial was announced in 2014, basic behavioral researchers (ranging from brain researchers to basic psychosocial researchers) were unaware that the changes would significantly impact their research until the three subsequent policies (GCP training, ClinicalTrials.gov registration, and clinical trial-specific FOAs/review criteria) were released in 2016 (Kaiser, 2017). Consequently, many of the perceived burdens for these policies were identified and

expressed in joint-society letters to the NIH. These joint-society letters were identified through the APS and the FABBS.

With respect to the revised clinical trial definition, the APS commented that the policy forces basic research with human subjects into the clinical trial definition (APS, 2018b). As a result, the APS expressed significant concern that the policy could place "undue burden" on researchers in terms of the application process, conduct of research, and monitoring of research (APS, 2017, 2018a). Similarly, the FABBS expressed concern that classifying such research a clinical trial would "impose a raft of new requirements" and "cripple exploratory research" (Kaiser, 2017). The FABBS outlined seven specific concerns (encompassing all new clinical trial policies) to the NIH. The perceived burdens identified by FABBS were: (1) definition of clinical trials includes basic science research; (2) basic scientists not consulted, yet impacted; (3) creating public confusion about the nature of studies in ClinicalTrials.gov; (4) NIH policy may decrease funding opportunities for basic scientists; (5) increases burden on investigators without a clear rationale; (6) penalties for noncompliance are significant; and (7) mandatory training is focused on clinical trials, not the type of research actually being funded and conducted (FABBS, 2017a).

Two perceived burdens were attributed to the clinical trial-specific FOAs and review criteria policy. First, an open letter to the NIH Director expressed concern that basic research applications now classified as clinical trials would be reviewed and scored by review panels who might not understand the nuances of basic discovery research which could potentially lead to lost research funding (FABBS, 2017a; Wolfe, 2017). Second, concerns were also expressed that difficulty identifying the appropriate funding opportunity announcement for clinical trials in basic science could delay funding and harm researchers (APS, 2016; FABBS, 2017a).

Two perceived burdens of the GCP training policy mandate were (1) the time commitment and (2) the training may have an inappropriate biomedical focus for basic behavioral science researchers (FABBS, 2017a).

Four potential burdens were identified resulting from the ClinicalTrials.gov registration and reporting policy. In the summary of public comments, NIH noted that some respondents were concerned that (1) the risks of burden and cost outweighed the benefit of transparency and (2) the timeline for reporting information was too short for academics with competing responsibilities at universities (NIH, 2016a). While multiple professional societies expressed support for the overarching goals of registration and results reporting for all human subjects research (clinical trials and non-trials alike), they noted additional perceived burdens: (3) monetary penalties for non-compliance and (4) researcher and public confusion resulting from using ClinicalTrials.gov rather than a platform designed for basic science research studies (FABBS, 2017b, 2018). The United States Congress noted these concerns and instructed NIH to delay inclusion of basic research studies under the policy until after the agency consulted with the community about how to suitably report results (Kaiser, 2018a).

Table 3. Summary of Potential Benefits and Burdens of NIH Clinical Trial Policies

Policy	Effective FY	Potential Benefits	Potential Burdens
Planning Post-Trial Access to Antiretroviral Treatments	2005	1. Reduces risk of treatment failure[1,2]	1. NIH does not pay for post-trial access[1] 2. Sets unequal expectations within patient community[5]
Revised Clinical Trial Definition	2016	1. Clarified definition[1] 2. Improved identification and tracking of clinical trials[1] 3. Improve review of applications[1] 4. Increased accountability, oversight, and transparency[1] 5. Reduce unnecessary duplication of effort[1]	1. New definition overlaps with basic research definition[6,7] 2. Confuses researchers and general public[6,7] 3. Subjects some basic science researchers to all clinical trial policies[6,7]
Clinical Trial-specific Funding Opportunity Announcements (FOA)	2019	1. Improved identification of clinical trials[1] 2. Improve information available to peer reviewers[1] 3. Uniformly apply trial-specific review criteria[1]	1. Loss/reduction in funding for basic science researchers[6,7] 2. Rejection of applications when submitted to incorrect FOA[6,7]
Good Clinical Practice Training Mandate	2017	1. Increase trial safety for participants[1] 2. Increase scientific rigor of trials[1] 3. Increase reliability of study data[1]	1. Time commitment[6,7] 2. Inappropriate focus for basic researchers[6,7]
ClinicalTrials.gov Registration and Reporting	2017 (Non-BESH[a]); 2021 (BESH[a])	1. More access to data for investigators and IRBs[1] 2. Better historical information for funding sponsors[1] 3. Ethical obligation for publicly-funded research data[1,3,4] 4. Advance knowledge base/reduce publication bias[1,3,4]	1. Cost[1] 2. Time commitment[6,7] 3. Monetary penalties for non-compliance[7] 4. Inappropriate repository/structure for basic science data[7]

[1] = NIH; [2] = (Shah et al., 2009); [3] = ICMJE; [4] = (Zarin et al., 2016); [5] = (Millum, 2011); [6] = Association for Psychological Science; [7] = Federation of Associations in Behavioral & Brain Sciences

[a]Basic Experimental Studies involving Humans (BESH)

NIH Responses to Concerns

Attempts by NIH to address some of the perceived burdens were identified. To address the concern that existing GCP training options were not geared toward basic behavioral research studies, the NIH partnered with the Society of Behavioral Medicine to develop a free GCP training module for the research community (OBSSR, 2017). To help researchers understand the revised clinical trial definition, NIH developed a series of decision aids and case studies to aid potential grant applicants with determining whether a research study is a clinical trial (NIH/OER, 2016). However, NIH acknowledged that some research studies simultaneously meet the federal definitions of basic research and clinical trial but noted that the NIH definition is consistent with similar definitions in the field (table 2). Those studies were named Basic Experimental Studies involving Humans (BESH) to allow for specific identification and assistance. BESH studies are those that "prospectively assign human participants to conditions (i.e., experimentally manipulate independent variables) and that assess biomedical or behavioral outcomes in humans for the purpose of understanding the fundamental aspects of phenomena without specific application towards processes or products in mind" (NIH, 2019b).

In July 2018, the NIH issued a policy notice entitled "Delayed Enforcement and Short-Term Flexibilities for Some Requirements Affecting Prospective Basic Science Studies Involving Human Participants" (NIH, 2018a). This notice delayed the requirement to register and report BESH studies in ClinicalTrials.gov until September 2019. During this delay, BESH clinical trials must still register and submit results, but can do so on a public platform designed for basic research. The policy enforcement delay also included an announcement that BESH-specific funding opportunity announcements would be published to reduce confusion. The policy delay was viewed as a positive step by the concerned societies (Kaiser, 2018b). The NIH issued a request for information in August 2018 to seek input regarding how best to implement the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information for prospective basic science studies involving human participants (BESH studies) (NIH,

2018c). While considering the comments received, the NIH continues to examine potential changes to ClinicalTrials.gov and has subsequently delayed the BESH study registration and reporting requirements to that platform until 2021 (NIH, 2019a; Wolinetz, Lauer, & Riley, 2019). Current (September 2019) clinical trial policy NIH requirements for standard (non-BESH) and BESH clinical trials are summarized in Table 4.

Table 4. Current Policy Requirements for all NIH Clinical Trials

Non-BESH Clinical Trial	**BESH Clinical Trial**
1. Funding application submitted to clinical trial-specific Funding Opportunity Announcement	1. Funding application submitted to BESH clinical trial-specific Funding Opportunity Announcement
2. Provision of key clinical trial information in funding application including data and safety monitoring plan	2. Provision of key clinical trial information in funding application including data and safety monitoring plan
3. DSMB oversight of multi-site clinical trials that entail potential risk to participants	3. DSMB oversight of multi-site clinical trials that entail potential risk to participants
4. Good Clinical Practice training for study staff	4. Good Clinical Practice training for study staff
5. Registration and results reporting to ClinicalTrials.gov	5. Registration and results reporting to ClinicalTrials.gov or existing basic science portals
6. Plan for post-trial access to antiretroviral treatment	

NIMH-specific Clinical Trial Policies

In addition to the NIH-wide clinical trial policies, the NIMH has also published five NIMH-specific clinical trial policies. These policies apply only to research that is funded by the NIMH and are summarized in Table 5. The first policy, entitled "NIMH Policy for Submission of Applications Containing Clinical Trials" required that clinical trial applications must be submitted to an NIMH clinical trial-specific funding opportunity announcement (NIMH, 2014b). This policy was effective for grants funded in FY2015. The policy is consistent with the NIH-wide clinical trial-specific FOA policy, but the requirement preceded the NIH-wide policy by four years. NIMH identified the intended benefit of this policy as improvement in efficiency, transparency, and human subject protection in clinical trials (Insel & Gogtay,

2014, 2015). One anticipated burden identified in the policy announcement was that clinical trial applications submitted to non-clinical trial FOAs would not be accepted for review or funding.

A second NIMH-specific clinical trial policy, entitled "Data Sharing Expectations for NIMH-funded Clinical Trials" went into effect in FY2015 (NIMH, 2014a). This funding policy established that NIMH-funded clinical trials would share data via a new common informatics platform developed by the NIMH. Given the concerns that NIMH-funded clinical trials were not publishing results in a timely manner, the NIMH proposed that this platform (and sharing mandate) would have significant value to the research community and accelerate scientific discovery (Brauser, 2014; NIMH, 2014a). Further, the financial cost of data sharing could be charged directly to the grant, thereby alleviating financial burden (NIMH, 2014a). While this data sharing policy briefly began as a clinical trial-specific policy, it was quickly expanded to all NIMH-funded research involving human subjects in subsequent policies which harmonized the clinical trial and non-trial expectations in FY2016 (NIMH, 2015a, 2019). Therefore, this policy is no longer a clinical trial-specific policy because the requirement now applies to all clinical research.

The third NIMH-specific clinical trial policy, entitled "NIMH Policy Governing the Monitoring of Clinical Trials" went into effect in FY2016 (NIMH, 2015b, 2015c). This policy built upon the NIH-wide requirement for data and safety monitoring in all clinical trials by stating the need for a clear and well-developed data and safety monitoring plan (DSMP), identifying the critical elements of a DSMP, outlining the appropriate levels of monitoring for a clinical trial, and assuring the NIMH is notified by NIMH-funded researcher of the outcomes of those monitoring activities (NIMH, 2015b).

In the same announcement, the NIMH issued the fourth NIMH-specific clinical trial policy, entitled "Policy Governing Independent Safety Monitors and Independent Data and Safety Monitoring Boards" which also went into effect in FY2016 (NIMH, 2015b). This policy clarified when and how

independent safety monitors (ISM) and data and safety monitoring boards (DSMB) should be used for NIMH-funded clinical trials (NIMH, 2015d). The goal of these two companion policies was to ensure the safety of research participants in NIMH-funded clinical trials.

The fifth NIMH-specific clinical trial policy, entitled "Change to NIMH Policy for Recruitment of Participants in Clinical Research" required all new clinical trial awards to establish recruitment milestones and report progress triannually effective FY2017 (NIMH, 2016). NIMH proposed that this policy improves oversight leading to successful recruitment and study completion. Previously, the policy only applied to human research studies with a sample size greater than 150 participants. This policy change expanded the scope to include all clinical trials regardless of size. NIH requires the establishment of recruitment milestones and progress reporting on an annual basis. The NIMH's triannual recruitment reporting policy is more frequent and preceded the NIH-wide tracking of clinical trial recruitment data in the annual progress report by two years.

Table 5. Summary of Intended Benefits and Anticipated Burdens of NIMH-Specific Clinical Trial Policies

Policy	**Effective FY**	**Intended Benefits**	**Anticipated Burdens**
NIMH Clinical Trial-specific Funding Opportunity Announcements (FOA)	2015	1. Improved efficiency, transparency, and human subject protection.	1. Rejection of applications submitted to incorrect FOA.
NIMH Data and Safety Monitoring Policy	2016	1. Increased human subject protection.	None identified.
NIMH ISM/DSMB Policy	2016	1. Increased human subject protection.	None identified.
Recruitment Monitoring and Reporting	2005: Sample size ≥150 2017: All clinical trials	1. Improve likelihood of successful study recruitment and completion.	None identified.

Note: Searches for potential benefits or burdens from non-NIMH sources returned no results. All potential benefits and potential burdens were identified from the NIMH policy notice or a companion NIMH-authored article.

Discussion

The NIH implemented five clinical trial policies between fiscal years 2005 and 2019. The NIMH implemented four clinical trial policies during the same time period. The results are consistent with the previously discussed adaptation of Donabedian's model. The NIH/NIMH policies were designed and implemented to build structure with the intent of improving processes and subsequently grant performance outcomes. Because the clinical trial policies are intertwined, common themes were identified for both potential benefits and potential burdens. The clinical trial definition policy, as the foundation for the subsequent policies in this analysis, was often discussed alongside the other individual policies. The NIH engaged stakeholders during implementation of some policies, but both NIH and NIMH should consider involving stakeholders earlier during development for future policies. In numerous articles, researchers and professional organizations noted that they were unaware of the forthcoming policy changes until after the policies were announced and were therefore unable to engage in the policymaking process. Both agencies should also consider building outcome evaluation into the policy development process.

The ubiquitous rationale for the recent clinical trial policies was the need for quality improvement of the identification, review, conduct, and output from NIH-funded research. Consequently, the NIH/NIMH saw these elements, along with increased human subject protection, as the intended benefits across all of the policies characterized in this study. Similarly, the basic behavioral science research community identified cross-cutting perceived burdens resulting from these policies. These repeating themes were loss of research time (through time spent troubleshooting unclear applications/forms, taking irrelevant mandated trainings, or navigating incompatible data repositories); potential loss of future research funding; and widespread confusion about a definition that seemed to suddenly envelope a previously distinct field. The intended benefits and perceived burdens repeat

across each clinical trial policy because the core disagreement begins (and to some degree ends) with the definition of a clinical trial.

The clinical trial definition was the most contentiously debated policy. The revised definition appears to capture a wider subset of studies than the previous definition. The policy definition is consistent with the other definitions currently used by other federal agencies and the ICMJE; however, unlike those definitions, the NIH's definition is operationalized to determine the applicability of administrative requirements and other NIH policies including DSMP/DSMB requirements, funding opportunity announcements, review criteria, GCP training, and ClinicalTrials.gov registration and results reporting requirements. Each of these policies is intended to push better identification, review, tracking, accountability, oversight, and transparency; increased rigor and participant safety; and better scientific progress through better science and data sharing. Despite these intended benefits, the lack of engagement with the research community, specifically basic behavioral researchers, has proven problematic. The revised clinical trial definition was not well discussed with stakeholders leading to confusion and general disagreement. Researchers have repeatedly expressed concerns that the new definition (and downstream applicability of other clinical trial policies) will result in confusion (for researchers and public); increased time burden for researchers; financial burden for grantees; and potential for miscommunication with the public over the very nature of clinical trials.

In response to the concerns of basic behavioral science researchers, the NIH implemented basic behavioral science focused GCP training, BESH-only FOAs, and flexibility for BESH clinical trial registration and results reporting. The NIH attempted to reduce the perceived burdens and address the concerns of the research community, but some concerns, such as administrative burden, continued to be expressed after these efforts. While it is unlikely that any policy change will please all stakeholders, the NIH could have worked with these groups during the policy development phase to build consensus

and agreement upon the rationale for the changes and necessary adjustments to accommodate a wider range of studies now considered clinical trials.

NIH did not plan for or evaluate objective measures of benefit or burden that could be used for future policy development or revision. Interestingly, the NIMH implemented clinical trial-specific FOAs in FY2015 – four years before NIH (2019). The NIMH also began participant recruitment tracking for many studies in 2005 and expanded this to all clinical trials in FY2017 (also preceding the NIH-wide policy). Much like NIH, the NIMH stated the intended benefit and rational for each of these policies, but unfortunately did not formally evaluate anticipated burdens of the NIMH-specific clinical trial policies (no public comments were identified either). Still, the early NIMH implementation of policies similar to the NIH policies represents an opportunity to evaluate the changes in outcomes due to the NIMH-specific policies as a prediction model for the later NIH-wide policies. For example, concerns that administrative burdens delay research can be examined by evaluating research participant recruitment progress for ongoing studies and time to result reporting (in ClinicalTrials.gov) in completed studies. Over time, the impact of the policies on research outcomes could also be evaluated through examining changes in clinical practice or impact on scientific influence through the Relative Citation Ratio (Hutchins, Yuan, Anderson, & Santangelo, 2016). Both NIH and NIMH should incorporate outcome evaluation into the policy development process.

There are a several limitations to this study. First, the identification of potential benefits and potential burdens is limited to existing published statements rather than direct surveying of key stakeholders. Consequently, first-hand experiences with burden of implementation and compliance were not within the scope of this study. Further, the intertwining nature of how these concerns were voiced (co-issued and/or repeat issued) limited the ability to discuss magnitudes or frequencies. Second, the lack of formal public comment on the NIMH-only policies limited the summary of potential burdens to only those that were anticipated by NIMH. Third, this study examines only NIH and NIMH

policies and does not include additional requirements from other federal agencies such as the Food and Drug Administration or the HHS Office for Human Research Protections. Finally, this descriptive study does not validate the identified statements of potential benefits or potential burdens.

Both the NIH and the NIMH have implemented clinical trial policies to build structure with the intent of influencing process and outcomes; however, neither NIH nor NIMH appear to have examined the potential burdens during early policy development. The NIH and NIMH should consider engaging stakeholders, through advisory groups or solicitation of public comment, during major policy development. NIH/NIMH should formally evaluate and discuss potential benefits/burdens in the policy rationale for future science policies. Further, both agencies should consider incorporating outcome evaluation into future policy development. Finally, both NIH and NIMH should consider post-implementation evaluation of the policy impact on researchers which may include direct surveys to measure the magnitude of actual benefits or burdens.

Appendix: Search Terms

The following search terms were used to identify benefits and burdens as described in the methods section. Data sources were searched individually for each term. The results were aggregated by hand.

Search terms:

"NOT-OD-05-038"

"Guidance for Addressing the Provision of Antiretroviral Treatment for Trial Participants Following their Completion of NIH-Funded HIV Antiretroviral Treatment Trials in Developing Countries"

"NOT-OD-15-015"

"Notice of Revised NIH Definition of "Clinical Trial"

"NOT-OD-16-147"

"Policy on Funding Opportunity Announcements (FOA) for Clinical Trials"

"NOT-OD-16-148"

"Policy on Good Clinical Practice Training for NIH Awardees Involved in NIH-funded Clinical Trials"

"NOT-OD-16-149"

"NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information"

"NOT-OD-18-212"

"Delayed Enforcement and Short-Term Flexibilities for Some Requirements Affecting Prospective Basic Science Studies Involving Human Participants"

"NOT-MH-14-007"

"NIMH Policy for Submission of Applications Containing Clinical Trials"

"NOT-MH-14-015"

"Data Sharing Expectations for NIMH-funded Clinical Trials"

"NOT-MH-15-012"

"Data Sharing Expectations for Clinical Research Funded by NIMH"

"NOT-MH-15-025"

"NIMH Policy Governing the Monitoring of Clinical Trials"

"NOT-MH-15-025"

"Policy Governing Independent Safety Monitors and Independent Data and Safety Monitoring Boards"

"NOT-MH-16-013"

"Change to NIMH Policy for Recruitment of Participants in Clinical Research"

References:

APS. (2016). Major Change in NIH Policy for Clinical Trials Applications. Retrieved from https://www.psychologicalscience.org/publications/observer/obsonline/major-change-in-nih-policy-for-clinical-trials-applications.html

APS. (2017, June 6, 2017). Re: Clarification of NIH Clinical Trial Policy. Retrieved from https://fabbs.org/wp-content/uploads/2017/10/APS-to-Dr.-Collins-re-clinical-trials-policy-6-6-17.pdf

APS. (2018a). Congress Stops NIH From Implementing New Clinical Trials Policy. Retrieved from https://www.psychologicalscience.org/publications/observer/obsonline/congress-stops-nih-from-implement-new-clinical-trials-policy.html

APS. (2018b). Make Your Voice Heard: Tell NIH You Oppose the Classification of Basic Human Subjects Research as Clinical Trials. Retrieved from https://www.psychologicalscience.org/policy/make-your-voice-heard-tell-nih-you-oppose-the-classification-of-basic-human-subjects-research-as-clinical-trials.html

Brauser, D. (2014, April 03, 2014). NIMH Tightens Up Funding Criteria for Clinical Trials. *Medscape Medical News*. Retrieved from https://www.medscape.com/viewarticle/823065

DHHS. (2017). Federal Policy for the Protection of Human Subjects ('Common Rule'). *45 CFR 46.* Retrieved from https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html

Donabedian, A. (2005). Evaluating the quality of medical care. 1966. *Milbank Q, 83*(4), 691-729. doi:10.1111/j.1468-0009.2005.00397.x

FABBS. (2017a, July 12, 2017). Letter to NIH-Collins Re Clinical Trials. Retrieved from https://fabbs.org/wp-content/uploads/2017/08/Letter-to-NIH-Collins-Re-Clinical-Trials-FINAL.pdf

FABBS. (2017b). Multi-Society Letter to NIH Director. Retrieved from https://fabbs.org/wp-content/uploads/2017/10/nih-clinical-trials-signon-10-27-17-final.pdf

FABBS. (2018). Multi-Society Letter to Deputy Director. Retrieved from https://fabbs.org/wp-content/uploads/2018/10/Tabak-Letter-Re-CTs-FINAL.pdf

G.A.O. (2016). *NATIONAL INSTITUTES OF HEALTH: Additional Data Would Enhance the Stewardship of Clinical Trials across the Agency*. (GAO-16-304). Retrieved from https://www.gao.gov/products/GAO-16-304.

Hudson, K. L., Lauer, M. S., & Collins, F. S. (2016). Toward a New Era of Trust and Transparency in Clinical Trials. *Jama, 316*(13), 1353-1354. doi:10.1001/jama.2016.14668

Hutchins, B. I., Yuan, X., Anderson, J. M., & Santangelo, G. M. (2016). Relative Citation Ratio (RCR): A New Metric That Uses Citation Rates to Measure Influence at the Article Level. *PLoS Biol, 14*(9), e1002541. doi:10.1371/journal.pbio.1002541

ICMJE. (n.d.-a). Clinical Trials. Retrieved from http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

ICMJE. (n.d.-b). Clinical Trials Registration. Retrieved from http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/

Insel, T. R., & Gogtay, N. (2014). National Institute of Mental Health clinical trials: new opportunities, new expectations. *JAMA Psychiatry, 71*(7), 745-746. doi:10.1001/jamapsychiatry.2014.426

Insel, T. R., & Gogtay, N. (2015). NIMH Clinical Trials: Portfolio, Progress to Date, and the Road Forward. Retrieved from https://www.nimh.nih.gov/funding/opportunities-announcements/clinical-trials-foas/nimh-clinical-trials-portfolio-progress-to-date-and-the-road-forward.shtml

Kaiser, J. (2017, July 19, 2017). Some scientists hate NIH's new definition of a clinical trial. Here's why. *Science Magazine*.
Kaiser, J. (2018a). Final 2018 budget bill eases biomedical researchers' policy worries. *Science Magazine*.
Kaiser, J. (2018b). NIH delays controversial clinical trials policy for some studies. *Science Magazine*.
Lauer, M. S., & Wolinetz, C. (2016). Building Better Clinical Trials through Stewardship and Transparency. Retrieved from https://nexus.od.nih.gov/all/2016/09/16/clinical-trials-stewardship-and-transparency/
Millum, J. (2011). Post-trial access to antiretrovirals: who owes what to whom? *Bioethics, 25*(3), 145-154. doi:10.1111/j.1467-8519.2009.01736.x
NIH. (2003). *NIH Grants Policy Statement*. Retrieved from https://grants.nih.gov/grants/policy/nihgps/nihgps_2003.pdf.
NIH. (2005). Guidance for Addressing the Provision of Antiretroviral Treatment for Trial Participants Following their Completion of NIH-Funded HIV Antiretroviral Treatment Trials in Developing Countries. *NOT-OD-05-038.*
NIH. (2014a). NIH Request for Public Comments on the Draft NIH Policy on Dissemination of NIH-Funded Clinical Trial Information. Retrieved from https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-019.html
NIH. (2014b). Notice of Revised NIH Definition of "Clinical Trial". *NOT-OD-15-015.* Retrieved from https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html
NIH. (2016a). NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information. *NOT-OD-16-149.* NOT-OD-16-149.
NIH. (2016b). Policy on Funding Opportunity Announcements (FOA) for Clinical Trials. Retrieved from https://grants.nih.gov/grants/guide/notice-files/not-od-16-147.html
NIH. (2016c). Policy on Good Clinical Practice Training for NIH Awardees Involved in NIH-funded Clinical Trials. Retrieved from https://grants.nih.gov/grants/guide/notice-files/not-od-16-148.html
NIH. (2017a). New NIH "FORMS-E" Grant Application Forms and Instructions Coming for Due Dates On or After January 25, 2018. Retrieved from https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-062.html
NIH. (2017b). Update on Clinical Trial Funding Opportunity Announcement Policy. Retrieved from https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-043.html
NIH. (2018a). Delayed Enforcement and Short-Term Flexibilities for Some Requirements Affecting Prospective Basic Science Studies Involving Human Participants. Retrieved from https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-212.html
NIH. (2018b, October 15, 2018). NIH Grants Policy Statement. Retrieved from https://grants.nih.gov/policy/nihgps/index.htm
NIH. (2018c). Request for Information (RFI): Registration and Results Reporting Standards for Prospective Basic Science Studies Involving Human Participants. Retrieved from https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-217.html
NIH. (2019a). Extension of Certain Flexibilities for Prospective Basic Experimental Studies With Human Participants. Retrieved from https://grants.nih.gov/grants/guide/notice-files/NOT-OD-19-126.html
NIH. (2019b). Glossary of NIH Terms. *NIH Glossary.* Retrieved from https://grants.nih.gov/grants/glossary.htm
NIH. (2019c). What We Do: Budget. Retrieved from https://www.nih.gov/about-nih/what-we-do/budget
NIH. (2019d). Who We Are. Retrieved from https://www.nih.gov/about-nih/who-we-are
NIH/OER. (2016, January 7, 2019). NIH Definition of Clinical Trial Case Studies. Retrieved from https://grants.nih.gov/policy/clinical-trials/case-studies.htm

NIH/OER. (2017a, September 8, 2017). Frequently Asked Questions: NIH Clinical Trial Definition. Retrieved from https://grants.nih.gov/grants/policy/faq_clinical_trial_definition.htm

NIH/OER. (2017b, July 26, 2017). Why Changes to Clinical Trial Policies? Retrieved from https://grants.nih.gov/policy/clinical-trials/why-changes.htm

NIMH. (2014a, Rescinded June 17, 2019). Data Sharing Expectations for NIMH-funded Clinical Trials. Retrieved from https://grants.nih.gov/grants/guide/notice-files/not-mh-14-015.html

NIMH. (2014b). NIMH Policy for Submission of Applications Containing Clinical Trials. Retrieved from https://grants.nih.gov/grants/guide/notice-files/not-mh-14-007.html

NIMH. (2015a, Rescinded June 17, 2019). Data Sharing Expectations for Clinical Research Funded by NIMH. Retrieved from https://grants.nih.gov/grants/guide/notice-files/not-mh-15-012.html

NIMH. (2015b, Replaced April 8, 2019). NIMH Clinical Research Policies and Guidance. Retrieved from https://grants.nih.gov/grants/guide/notice-files/NOT-MH-15-025.html

NIMH. (2015c, April 16, 2015). NIMH Policy Governing the Monitoring of Clinical Trials. Retrieved from https://www.nimh.nih.gov/funding/clinical-research/nimh-policy-governing-the-monitoring-of-clinical-trials.shtml

NIMH. (2015d, April 24, 2015). Policy Governing Independent Safety Monitors and Independent Data and Safety Monitoring Boards. Retrieved from https://www.nimh.nih.gov/funding/clinical-research/policy-governing-independent-safety-monitors-and-independent-data-and-safety-monitoring-boards.shtml

NIMH. (2016). NIMH Recruitment of Participants in Clinical Research Policy. Retrieved from https://www.nimh.nih.gov/funding/grant-writing-and-application-process/nimh-recruitment-of-participants-in-clinical-research-policy.shtml

NIMH. (2019, June 17, 2019). Notice of Data Sharing Policy for the National Institute of Mental Health. Retrieved from https://grants.nih.gov/grants/guide/notice-files/NOT-MH-19-033.html

OBSSR. (2017, January 25). The Society of Behavioral Medicine makes available the Good Clinical Practice Training (GCP). Retrieved from https://obssr.od.nih.gov/the-society-of-behavioral-medicine-has-made-available-the-good-clinical-practice-training-gcp/

Shah, S., Elmer, S., & Grady, C. (2009). Planning for posttrial access to antiretroviral treatment for research participants in developing countries. *Am J Public Health, 99*(9), 1556-1562. doi:10.2105/ajph.2008.157982

Taichman, D. B., Backus, J., Baethge, C., Bauchner, H., de Leeuw, P. W., Drazen, J. M., . . . Wu, S. (2016). Sharing Clinical Trial Data: A Proposal From the International Committee of Medical Journal Editors. *Jama, 315*(5), 467-468. doi:10.1001/jama.2015.18164

WHO, W. H. O. (n.d.). International Clinical Trials Registry Platform (ICTRP). Retrieved from https://www.who.int/ictrp/en/

Wolfe, J. e. a. (2017). OPEN LETTER TO NIH DIRECTOR FRANCIS COLLINS. Retrieved from https://fabbs.org/wp-content/uploads/2017/10/Letter-to-NIH-Collins-Re-Clinical-Trials-Signed.pdf

Wolinetz, C., Lauer, M., & Riley, W. (2019). Continuing to Work with the Community on Registration and Results Reporting for Basic Experimental Studies involving Humans. Retrieved from https://nexus.od.nih.gov/all/2019/07/24/continuing-to-work-with-the-community-on-registration-and-results-reporting-for-basic-experimental-studies-involving-humans/

Zarin, D. A., Tse, T., Williams, R. J., & Carr, S. (2016). Trial Reporting in ClinicalTrials.gov — The Final Rule. *New England Journal of Medicine, 375*(20), 1998-2004. doi:10.1056/NEJMsr1611785

Manuscript 2: Evaluating the Impact of the 2005 National Institute of Mental Health Policy for the Recruitment of Participants in Clinical Research on Relative Citation Ratios

Abstract

Background: The National Institutes of Health (NIH) has implemented policies to improve the rigor and conduct of clinical trials. Beginning in fiscal year 2019, the NIH now requires the establishment of recruitment milestones and periodic reporting of recruitment progress for clinical trial grants. While this policy is too recent for adequate impact evaluation, the National Institute of Mental Health (NIMH), a component of NIH, implemented a similar policy requiring recruitment milestones and progress reporting in fiscal year 2006 for NIMH-funded research. Evaluation of the NIMH policy can provide insight into the likely effects of the NIH-wide policy.

Methods: An observational, single-group, pre/post evaluation of the association between the NIMH Policy for the Recruitment of Participants in Clinical Research and the Relative Citation Ratio was conducted for non-fellowship, competing clinical trial grants funded by the NIMH from fiscal years 2004-2007. The association between the recruitment policy and the mean and maximum Relative Citation Ratios was examined through a multiple linear regression, adjusting for total grant cost, trial target sample size, grantee institution size, funding mechanism, and trial design.

Results: 124 clinical trial grants were identified. After adjusting for covariates, the clinical trial grants subject to the NIMH recruitment monitoring policy were associated with a statistically significant mean-per-grant citation ratio (citations relative to the field norm) 1.984 times that of the clinical trial grants that were not subject to the policy (p=0.005; 95% CI: [1.232, 3.196]). The clinical trial grants subject to the policy were also associated with a non-statistically significant 1.581 times maximum-per-grant citation ratio compared to the clinical trial grants not covered by the policy (p=0.246; 95% CI: [0.726, 3.440]).

Conclusions: The NIMH Recruitment Monitoring and Reporting policy was associated with a statistically significant increase in the mean-per-grant Relative Citation Ratio. These NIMH-specific results suggest that the NIH-wide requirements for recruitment milestones and progress monitoring might also be positively associated with improved Relative Citation Ratio. Increased Relative Citation Ratios generally reflect more impactful research.

Introduction

The National Institutes of Health (NIH) has developed and implemented a comprehensive suite of policy initiatives to "ensure rigor, transparency, and effectiveness of the US federally-funded clinical trial enterprise" (Lauer & Wolinetz, 2016; NIH/OER, 2017). One of these policies requires that grant applicants submit key information about a proposed clinical trial, including recruitment milestones, in the funding application and submit this application to a clinical trial-specific funding opportunity announcement (NIH, 2016). Once an application has been funded, the NIH requires that funded researchers submit Research Performance Progress Reports to the NIH on an annual basis to track the conduct of clinical trials (NIH/OER, 2018).

The Research Performance Progress Report process allows the NIH Program Officer to monitor the progress of the research study towards completion of the aims. The Program Officer is the NIH staff member responsible for the "programmatic, scientific, and/or technical aspects of a grant" (NIH, n.d.). Part of this responsibility includes monitoring study enrollment progress toward the participant recruitment target. Beginning in fiscal year (FY) 2019, Research Performance Progress Reports for clinical trials were required to report recruitment progress toward recruitment target milestones on at least an annual basis. Because a clinical trial is designed with a sample size that provides sufficient power to detect an effect of the intervention (Jones, Carley, & Harrison, 2003), failure to reach recruitment targets can render many trials powerless to answer the research question.

To avoid the consequences of under-recruitment, the NIH Program Officer (who oversees grant implementation) can take remediation actions to "course correct" grants that are falling behind on recruitment targets. Examples of remediation actions include increased frequency of reporting (e.g., moving from annually to quarterly or monthly), restructuring the release of funds for expenditure (i.e., restricting or delaying future funds until improvement is seen), or administrative supplements (additional funds to address unforeseen cost increases within the scope of the funded grant). For most Institutes/Centers, the default recruitment reporting period is annually. While monitoring recruitment progress is a key aspect of clinical trial stewardship, it also requires additional time and effort from both the researcher and NIH staff.

Because the NIH-wide policy was recently implemented, it is not yet possible to evaluate the impact of this policy on grant performance and research outcomes. However, while this NIH-wide policy became effective in FY2019, the National Institute of Mental Health (NIMH), a component of the NIH, was an early adopter of a comparable policy. In 2005, the NIMH published the NIMH Policy for the Recruitment of Participants in Clinical Research. This policy mandated tracking recruitment of participants in clinical research studies with a planned sample size of greater than 150 participants in the NIMH Recruitment Milestone Reporting System as of FY2006 (NIMH, 2005). While the NIMH policy's default recruitment monitoring reporting period is triannual as compared to the NIH default of annual monitoring, the focus of both policies is the establishment of recruitment milestones and regular reporting of progress toward those milestones. Further, the remediation options available to program officers are consistent under both policies. Therefore, the NIMH recruitment monitoring policy can be used as a proxy to forecast the potential impact of the NIH-wide recruitment monitoring policy.

This research examines the correlation between the implementation of the recruitment monitoring policy and a research outcome metric known as the Relative Citation Ratio (Hutchins, Yuan, Anderson, & Santangelo, 2016). A single group pre/post evaluation was conducted to evaluate the

association between the policy and the Relative Citation Ratio of publications resulting from clinical trial grants funded by the NIMH from FY2004 through FY2007. Given the premise that regular recruitment progress monitoring and remediation should improve the likelihood of successful recruitment completion and the notion that successful recruitment leads to sufficient statistical power to answer the research question, it was hypothesized that the recruitment monitoring policy will be associated with better grant performance outcomes as measured by an increase in the Relative Citation Ratio.

Methods

Study Overview

The design of this study is an observational single-group pre/post evaluation of the association between the NIMH Policy for the Recruitment of Participants in Clinical Research and the mean-per-grant and maximum-per-grant Relative Citation Ratios. This policy became effective beginning with FY2006 grants (NIMH, 2005); therefore, the study will compare outcomes among clinical trials funded in FY2004 and FY2005 to outcomes among clinical trial grants funded in FY2006 and FY2007. The primary outcome is a measure of research performance known as the Relative Citation Ratio or RCR (Hutchins et al., 2016). It is hypothesized that the recruitment reporting policy will improve both mean and maximum grant Relative Citation Ratios.

Study Sample

The study sample was comprised of grants that met the following eligibility criteria: (1) new competing applications and competing renewals (i.e., applications seeking new years of funding for new aims) for non-fellowship research grants; (2) awarded by NIMH from FY2004-2007; (3) self-identified as clinical trials; (4) with a planned sample size of at least 150 human participants (a criterion for applicability of the NIMH policy of interest); and (5) had Relative Citation Ratio data available in the iCite

database. Key demographics and grant performance outcomes were collected for each grant in the sample. These data were analyzed for a relationship between the implementation of the recruitment monitoring policy and the grant performance outcome measure.

Clinical trial grants were identified using the NIH's IMPAC II database using the Query View Report search interface. Grant characteristics were identified using the IMPAC II database and Research Portfolio Online Reporting Tools (NIH, 2019). The Relative Citation Ratio was identified from the NIH Office of Portfolio Analysis's iCite tool (NIH/OPA, 2016).

Measures

The independent variable (the NIMH recruitment policy) became effective at the beginning of FY2006. Grants applications were subject to the policy if initially awarded in FY2006 or later. The dependent variable (Relative Citation Ratio) was obtained for the sample of grants described. The Relative Citation Ratio (RCR) is "a field-normalized metric that shows the scientific influence of one or more articles relative to the average NIH-funded paper" (NIH/OPA, 2016). More simply stated, the metric is a ratio of the number of citations/year for a publication or group of publications compared to the average number of citations/year for all publications in that field of research. A ratio of "1" indicates that the publication(s) was cited with the same frequency as other publications in the field. A value of greater than 1 indicates that the publication was more highly cited than others in the field (ergo it is more "influential" than other publications by the field). Because most grants will result in multiple publications, two versions of the Relative Citation Ratio were used. The first outcome, mean RCR, is the average Relative Citation Ratio of all publications resulting from the grant. The second outcome, maximum RCR, is the highest single Relative Citation Ratio value from any single publication resulting from the grant. Both outcomes yield valuable information. The mean RCR demonstrates total grant productivity across all publications, but it may dilute the impact of the primary publication with less-

impactful secondary publications or protocol publications. The maximum RCR will show the impact of the single most prominent publication from a grant. This is likely to be the publication associated with the primary outcome analysis.

The analyses controlled for the following variables as potential confounders: total grant cost, trial target sample size, grantee institution size, funding mechanism, and trial design. Total grant cost and trial target sample size were continuous numeric variables. Grantee institution size was defined as the size of the research portfolio at a given research organization. Each organization was labeled categorically as either less than x<$200,000,000 USD, $200,000,000 ≤ x < $400,000,000, or x ≥ $400,000,000 USD in total FY2006 NIH funding. Funding mechanism was a categorical variable that represented the different types of grant mechanisms (e.g., R01, U01, or U10). Trial design, also a categorical variable, represented study design types such as randomized controlled trial, cluster randomized controlled trial, and pre/post trial.

Data Abstraction

Sample Identification and Abstraction

The clinical trial grants were identified through a Query View Report search of the internal NIH IMPAC II grant database. The database was searched for NIMH grants competitively funded from FY2004-2007 with the word "trial" in the text of the grant application title, abstract, or aims. This information was exported to a Microsoft Excel spreadsheet. Fellowship awards were excluded from the sample. Each grant was then manually reviewed to determine whether it was self-identified by the applicant as a clinical trial. If not, the record was excluded. Next, each grant was reviewed to determine the planned sample size. Proposals with fewer than 150 subjects were not covered by the NIMH policy and therefore were excluded. These data were recorded in the Excel spreadsheet.

Covariate Identification and Abstraction

Each grant application was reviewed to determine the clinical trial design and planned sample size. The Query View Report search results also returned the total grant award cost, grantee institution name, fiscal year, and funding mechanism for the identified sample of clinical trials. Grantee institution size was determined cross-referencing the grantee institution name with the total NIH funding in FY2006 identified in the NIH Research portfolio Online Reporting Tool (https://report.nih.gov/award/index.cfm).

Outcome Identification and Abstraction

The mean and maximum Relative Citation Ratio values were identified by searching the grant number in the iCite database (NIH/OPA, 2016). The mean RCR for all publications and the highest RCR for any publication associated with each grant was recorded in the excel spreadsheet. If no publication information was available, the grant was excluded from the sample.

Analysis

A multiple linear regression was conducted to evaluate the association between the recruitment reporting policy and the mean Relative Citation Ratio for each grant. A second multiple linear regression was conducted to examine the association of the recruitment reporting policy with the maximum Relative Citation Ratio for each grant. The Relative Citation Ratios were log-transformed to establish a normal distribution. The relationship between the policy and Relative Citation Ratio was adjusted for fiscal year, total grant award cost, grantee institution size, trial target sample size, funding mechanism, and clinical trial design. These analyses were conducted using Stata/IC Version 14.2 (StataCorp, 2015).

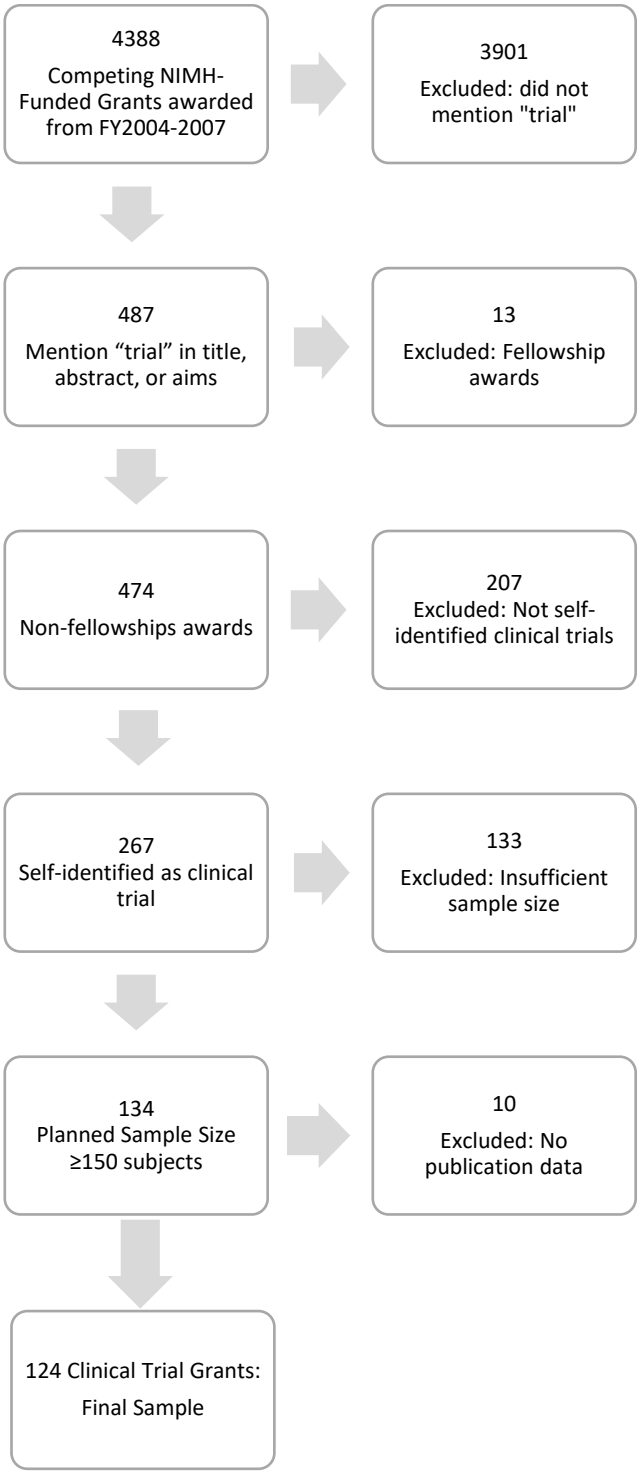
Limitations

A number of limitations to this study exist and warrant further exploration. First, this study was designed to examine correlation and does not prove a causal pathway. Second, the study did not examine the degree to which individual clinical trial grants complied with the policy nor did it assess the extent to which recruitment milestones (or the planned enrollment goals) were met. Third, this study examined only NIMH-funded clinical trials with a planned sample size of at least 150 participants. Fourth, the study did not account for historically high/low performing researchers/research teams. Fifth, this study did not evaluate the impact of trial outcomes (i.e., positive versus negative findings) on relative citation ratio.

Results

The study sample selection process is outlined in Figure 1. Of the 4,388 NIMH-funded competitive research grants funded from FY2004-2007, 487 mentioned the word "trial" in the title, abstract, or aims. Thirteen of these grants were fellowships and 474 were non-fellowship grants. 267 grants self-identified the study as a clinical trial in the grant application. 134 of those grants had a planned sample size of at least 150 human subjects. Ten grants did not have publications properly linked to the grant number. This is a limitation of the data. Individual publications and/or references to manuscripts were found for eight of those ten grants, but inclusion of the relative citation ratio outcomes for only the papers found by manual identification would have introduced bias; therefore, these ten grants were excluded from the analysis. The remaining 124 grants were the sample for this analysis.

Figure 1: Sample Selection



Sample Demographics

The clinical trial sample demographics are displayed by fiscal year in Table 1. Between 26 and 40 clinical trials with planned sample sizes of at least 150 participants were funded each year. The most frequent clinical trial design, by far, was an individually-randomized controlled trial design (110 out of 124). Twelve of the remaining trials were cluster-randomized controlled trials and two were pre/post trials. Pre/post (or pre-post) trials are prospective intervention studies without a control group (Thiese, 2014). Similarly, a research grant mechanism (e.g., R01, R34, etc.) was the most frequent mechanism with 95 of 124 trials in the sample. Cooperative agreements, or U-mechanisms, were the next most common with 26 of 124 trials. Across the four fiscal years, the mid-size and larger grantees received 70 of the 124 trials. The planned sample sizes ranged from 150 participants to 5,920 participants with a mean of 485. The mean sample size per fiscal year is also displayed in table 1.

The maximum Relative Citation Ratio, or the highest RCR for any single publication associated for a grant, ranged between 0.32 and 47.76 with a mean of 7.78. As noted previously, a value of less than 1 indicates that the publication was less-cited than the average publication in that field. The mean and range of the single-publication maximum values are displayed by fiscal year in table 1. For all publications associated with a grant, the mean RCR was 2.24 with a range between 0.32 and 5.86.

Table 1. Sample Demographics by Fiscal Year

Fiscal Year	2004	2005	2006	2007
n	28	26	40	30
Clinical Trial Design				
Cluster RCT	6	1	3	2
Pre/Post	1	1	0	0
RCT	21	24	37	28
Funding Mechanism				
Career Development Awards (K)	1	2	0	0
Research Grants (R)	22	20	25	28
Cooperative Agreements (U)	5	4	15	2
Grantee size				
x<$200,000,000 USD	8	11	19	16
$200,000,000≤x<$400,000,000 USD	7	9	7	7
x≥$400,000,000 USD	13	6	14	7
Maximum Relative Citation Ratio				
Mean	8.53	8.55	7.06	6.84
Range	1.40 - 47.46	0.62 - 41.06	0.32 - 34.81	0.54 - 45.48
Mean Relative Citation Ratio				
Mean	1.96	2.14	2.87	1.74
Range	0.79 - 5.30	0.46 - 5.05	0.32 - 5.86	0.45 - 3.77
Average Total Award Cost	$ 2,583,064	$ 2,258,076	$ 1,902,647	$ 2,822,873
Average Planned Sample Size	871	403	298	446

Regression Analyses

The mean RCR and maximum RCR values were analyzed and determined to be non-normally distributed by histogram, Shapiro-Wilk test, and Q-Q plot. The mean and maximum RCR values were log-transformed to establish a normal distribution. The log-transformed distribution of mean RCR and

maximum RCR was confirmed as normal with the Shapiro-Wilk test, kernel density plot of studentized residuals, and Q-Q plot. No severe outliers were identified. Following multiple linear regression, the coefficients and confidence intervals were exponentiated and displayed in Table 2.

Mean RCR Regression

A multiple linear regression was performed to investigate whether the implementation of the recruitment monitoring policy could significantly predict the average Relative Citation Ratio of publications associated with a given clinical trial grant. The results of the regression indicated that the model explained 23.3% of the variance and that the model was a significant predictor of mean Relative Citation Ratio. The implementation of the recruitment milestone reporting policy was associated with a 1.984 increase in mean per-grant Relative Citation Ratio (p=0.005; 95% CI: [1.232, 3.196]) when adjusting for grantee size, total grant award cost, planned sample size, fiscal year, funding mechanism, and clinical trial design. Fiscal year and the R43 funding mechanism were also positively associated with mean RCR. The reference case for funding mechanism was the R01 mechanism. Grantee size, total award cost, planned sample size, and clinical trial design did not have statistically significant associations with mean RCR.

Maximum RCR Regression

A second multiple linear regression was performed to investigate whether the implementation of the recruitment monitoring policy could significantly predict the maximum Relative Citation Ratio of any publication associated with a given clinical trial grant. The results of the regression indicated that the model explained 16.7% of the variance but the model itself was not a significant predictor of maximum Relative Citation Ratio at the α=0.05 level (p=0.1423). Under this model, the implementation

of the recruitment milestone reporting policy was associated with a 1.581 increase in the maximum per-grant Relative Citation Ratio (p=0.246; 95% CI: [0.726, 3.440]) when adjusting for grantee size, total grant award cost, planned sample size, fiscal year, funding mechanism, and clinical trial design. The R43 funding mechanism was positively associated with an increased maximum Relative Citation Ratio as shown in table 2. The reference case for funding mechanism was the R01 mechanism.

Table 2. Results of Multiple Linear Regression Analyses for Mean Grant and Maximum Grant Relative Citation Ratios

	Mean Grant Relative Citation Ratio[a]				Maximum Grant Relative Citation Ratio[b]			
	β	*P* value	[95% Confidence Interval]		β	*P* value	[95% Confidence Interval]	
Recruitment Policy[1]	1.984	0.005**	1.232	3.196	1.581	0.246	0.726	3.440
Grantee Size[2]								
x<$200,000,000USD	REF	REF	REF	REF	REF	REF	REF	REF
$200,000,000USD≤x<$400,000,000	1.000	0.998	0.767	1.304	1.051	0.821	0.682	1.618
x≥$400,000,000USD	0.884	0.340	0.686	1.140	0.909	0.650	0.601	1.376
Total Award Cost	1.000	0.361	1.000	1.000	1.000	0.403	1.000	1.000
Planned Sample Size	1.000	0.360	1.000	1.000	1.000	0.896	1.000	1.000
Fiscal Year	0.738	0.006**	0.595	0.917	0.753	0.114	0.529	1.072
Funding Mechanism[3]								
R01	REF	REF	REF	REF	REF	REF	REF	REF
K (Career Development)	1.625	0.203	0.767	3.442	2.665	0.115	0.784	9.063
R15	0.843	0.698	0.353	2.014	0.443	0.258	0.107	1.831
R21	0.471	0.206	0.146	1.522	0.257	0.162	0.038	1.740
R34	1.667	0.053	0.993	2.799	0.867	0.739	0.373	2.019
R43	0.158	0.002**	0.049	0.512	0.061	0.005**	0.009	0.414
U01	1.208	0.290	0.849	1.720	0.890	0.689	0.500	1.582
U10	0.564	0.104	0.282	1.127	0.777	0.659	0.251	2.402
Clinical Trial Design								
RCT[3]	REF	REF	REF	REF	REF	REF	REF	REF
Cluster RCT[4]	0.831	0.441	0.518	1.334	0.807	0.584	0.373	1.746
Pre/Post Trial	0.583	0.229	0.241	1.410	0.292	0.093	0.069	1.233

[a]Mean Relative Citation Ratio of all publications for each grant

[b]Highest Relative Citation Ratio of any publication for each grant

[1]NIMH Recruitment Milestone Reporting Policy; [2]Grantee's total NIH funding in FY2006;

[3]Individually-randomized control trial; [4]Cluster-randomized control trial.

*:0.01≤P≤0.05

**:0.001≤P≤0.01

Discussion

This study investigated the association between a NIMH policy requiring the establishment of recruitment milestones and progress reporting with grant performance outcomes. The hypothesis was that the implementation of this recruitment policy would be correlated with improved clinical trial grant performance as demonstrated by an increase in mean and maximum Relative Citation Ratios. This

hypothesis was based upon three logical assumptions: (1) establishing recruitment milestones and monitoring progress toward said milestones would increase the likelihood of reaching those milestones, (2) studies that reach their recruitment targets are more likely to have statistical power to test their research hypothesis, and (3) research adequate statistical power is more valued by fellow researchers than underpowered research. Findings from this study suggest a positive association between the implementation of the recruitment monitoring and reporting policy and both the mean and maximum Relative Citation Ratio; however, only the positive association with the mean Relative Citation Ratio was statistically significant.

The finding that the recruitment monitoring policy was associated with an increase in mean relative citation ratio suggests that the scientific community found the publications resulting from the trials covered by the recruitment monitoring policy to be, on average, more valuable (and therefore worth referencing) than those not covered by the policy. As previously mentioned, studies that under-recruit are less likely to have statistical power to answer their research questions. If we assume that enhanced attention to recruitment increases the likelihood of sufficient recruitment, then the higher mean RCR may illustrate that these trials achieved statistical power to answer the research questions and publish results.

Unlike the mean RCR association, the positive association between the recruitment policy and the maximum RCR was not statistically significant. If the mean RCR represents the influence of all publications from the grant as a whole, then the maximum RCR can be understood as a measure of the single most influential publication from with each clinical trial grant. The non-significant finding suggests that, while the policy may be associated with more influential research, the single-most influential publication may be correlated to something other than the policy. One possibility includes bias toward publication and citation of positive results. Previous research has shown that positive outcomes are more likely to be cited than negative outcomes; therefore, the maximum RCR per grant

may be influenced by whether the study findings were positive (de Vries et al., 2018; Duyx, Urlings, Swaen, Bouter, & Zeegers, 2017; Jannot, Agoritsas, Gayet-Ageron, & Perneger, 2013). Positive versus negative trial outcomes were not accounted or adjusted for in this analysis and should be investigated further.

The initial premise for examining this relationship was not just to identify the association between the NIMH recruitment monitoring policy and the impact on NIMH clinical trial grant outcomes. While this is useful information for the NIMH as a funding agency, the broader goal was to forecast the impact of the FY2019 NIH-wide policy that requires establishment of recruitment milestones and periodic (at least annual) reporting of recruitment progress. In this study, the NIMH policy was viewed as a proxy for the subsequent NIH-wide policy. The NIMH policy requires the establishment of recruitment milestones and triannual reporting on progress toward those milestones. The NIH policy requires at least annual milestones and recruitment progress reporting (with the option for NIH staff to choose more frequent time intervals). Both policies establish a premise of target milestones and periodic reporting of progress toward those targets. If we accept that the NIMH and NIH policies are similar, then we can infer that the results of this study suggest a positive association would be observed between the implementation of the FY2019 NIH-wide policy and the mean Relative Citation Ratio (and discount the notion that the administrative burden of regular recruitment monitoring is harmful to research progress). Further studies are recommended to examine the impact of compliance on the association, the association with smaller clinical trials, and the association for trials in other scientific disciplines to increase the generalizability of these results.

References

de Vries, Y. A., Roest, A. M., de Jonge, P., Cuijpers, P., Munafo, M. R., & Bastiaansen, J. A. (2018). The cumulative effect of reporting and citation biases on the apparent efficacy of treatments: the case of depression. *Psychol Med, 48*(15), 2453-2455. doi:10.1017/s0033291718001873

Duyx, B., Urlings, M. J. E., Swaen, G. M. H., Bouter, L. M., & Zeegers, M. P. (2017). Scientific citations favor positive results: a systematic review and meta-analysis. *J Clin Epidemiol, 88*, 92-101. doi:10.1016/j.jclinepi.2017.06.002

Hutchins, B. I., Yuan, X., Anderson, J. M., & Santangelo, G. M. (2016). Relative Citation Ratio (RCR): A New Metric That Uses Citation Rates to Measure Influence at the Article Level. *PLoS Biol, 14*(9), e1002541. doi:10.1371/journal.pbio.1002541

Jannot, A. S., Agoritsas, T., Gayet-Ageron, A., & Perneger, T. V. (2013). Citation bias favoring statistically significant studies was present in medical research. *J Clin Epidemiol, 66*(3), 296-301. doi:10.1016/j.jclinepi.2012.09.015

Jones, S. R., Carley, S., & Harrison, M. (2003). An introduction to power and sample size estimation. *Emergency Medicine Journal, 20*(5), 453-458. doi:10.1136/emj.20.5.453

Lauer, M. S., & Wolinetz, C. (2016). Building Better Clinical Trials through Stewardship and Transparency. Retrieved from https://nexus.od.nih.gov/all/2016/09/16/clinical-trials-stewardship-and-transparency/

NIH. (2016). Policy on Funding Opportunity Announcements (FOA) for Clinical Trials. Retrieved from https://grants.nih.gov/grants/guide/notice-files/not-od-16-147.html

NIH. (2019). Research Portfolio Online Reporting Tools (RePORT). Retrieved from https://report.nih.gov/

NIH. (n.d.). Glossary of NIH Terms. Retrieved from https://grants.nih.gov/grants/glossary.htm#ProgramOfficialPOProgramOfficerProjectOfficer

NIH/OER. (2017, July 26, 2017). Why Changes to Clinical Trial Policies? Retrieved from https://grants.nih.gov/policy/clinical-trials/why-changes.htm

NIH/OER. (2018, May 8, 2018). Research Performance Progress Report (RPPR). Retrieved from https://grants.nih.gov/grants/rppr/index.htm

NIH/OPA. (2016). iCite. online. Retrieved from https://icite.od.nih.gov/

NIMH. (2005). Terms and Conditions for Recruitment of Participants in Clinical Research. Retrieved from https://www.nimh.nih.gov/funding/grant-writing-and-application-process/terms-and-conditions-for-recruitment-of-participants-in-clinical-research.shtml

StataCorp. (2015). Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.

Thiese, M. S. (2014). Observational and interventional study design types; an overview. *Biochemia medica, 24*(2), 199-210. doi:10.11613/BM.2014.022

Manuscript 3: Evaluating the Impact of the Revised National Institutes of Health Clinical Trial Definition on Recruitment Progress

Abstract

Background: The National Institutes of Health (NIH) announced a revised definition of "clinical trial" in 2014 to improve trial identification and administrative compliance. Researchers and professional groups have voiced concerns that the revised definition will add administrative burden that will slow research progress. The National Institute of Mental Health (NIMH), a component of NIH, began systematically identifying and tracking grants that met the revised clinical trial definition in 2015 (four years prior to the development of an NIH-wide system in 2019). Evaluation of the policy's effect on recruitment progress in NIMH-funded grants may forecast the NIH-wide effect.

Methods: A quasi-experimental study examined the effect of the new clinical trial definition policy on recruitment progress in grants. The study used a difference-in-differences design comparing recruitment progress before and after the policy took effect in a group of studies newly identified as clinical trials under the policy relative to a comparison group of clinical trials unaffected by the new policy. The primary outcome was a measure of on-pace recruitment progress toward milestone targets. The relationship between the policy and recruitment progress was examined through a multiple logistic regression, adjusting for fiscal year, NIMH funding division, grant funding, ClinicalTrials.gov registration, trial sample size, and total NIH funding awarded to a grantee institution.

Results: A total of 132 clinical trial grants were identified and analyzed. There were 90 grants in the intervention group and 42 grants in the control group. Within the intervention group, 52 grants were impacted by the revised definition policy. After adjusting for covariates, the difference-in-differences in recruitment progress before and after the policy change between the control and intervention groups was not significant. Trials led by researchers at institutions receiving more than $400,000,000 in funding from NIH had significantly higher odds of meeting recruitment targets (OR: 4.95; 95% CI: 1.63-15.01).

Conclusions: The NIH revised clinical trial definition had no clear effect on recruitment progress in newly-identified NIMH-funded clinical trials as compared to traditionally-identified clinical trials. Therefore, this study did not find evidence supporting the concern that revised clinical trial definition would delay research progress. Further research is needed to evaluate other implications of the policy.

Introduction

In late October 2014, the National Institutes of Health (NIH) announced a policy revising the definition of "clinical trial" as the beginning of an effort to ensure that all clinical trials are correctly identified, properly conducted, and that the results are reported promptly to share the knowledge gained with the public (Hudson, Lauer, & Collins, 2016). The previous definition used by NIH was "a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices)" (Reif-Lehrer, 2005). The prior definition was considered vague; therefore, the NIH revised the definition to "a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes" (NIH, 2014). The revised definition is consistent with the definitions issued by the World Health Organization, International Committee of Medical Journal Editors (ICMJE), and other United States governmental research agencies (DHHS, 2017; ICMJE, n.d.; WHO, n.d.); however, the NIH also uses this definition in other policies to determine the applicability of numerous administrative requirements such as good clinical practice training and ClinicalTrials.gov registration and results reporting (APS, 2017, 2018; Kaiser, 2017). This revision also expanded the range of studies that are classified as a clinical trial.

The revised definition policy was met with resistance from researchers in the basic behavioral and social science fields who felt the expansion would force unnecessary compliance burdens on their studies including clinical trial registration, results reporting, and a "massive amount of dysfunction and paperwork" (Kaiser, 2017). The concerns were that the associated clinical trial policies are onerous and impose biomedical clinical research standards on non-biomedical study designs (FABBS, 2017; Kaiser, 2017). While general agreement exists on NIH's overall goals of better science, those opposed to the policy changes warned that burdensome or incongruous requirements would slow or even halt the progress of science (NIH, 2016).

The NIH clinical trial definition has been a subject of much debate over the last three years. To date, the arguments (for and against) the revised definition have been made on anecdotal experiences of researchers, regulators, funders, policy makers, and the general public. No formal evaluation has been conducted on the impact of this policy change on grant progress. To evaluate whether administrative burden of clinical trial policies based on the revised clinical trial definition delayed grant progress, this study examined the relationship between the clinical trial definition policy and study recruitment progress. Potential delays in study startup and conduct can be identified by examining the progress of study recruitment toward a priori milestones.

Although the revised definition was announced in 2014 and effective for NIH-funded research beginning in fiscal year (FY) 2016, many NIH Institutes/Centers did not have the capacity to identify and track all clinical trials (using the revised definition) until an NIH-wide system was implemented in FY2019. However, the National Institute of Mental Health (NIMH), an institute within of the NIH, identified grants that met the revised clinical trial definition and tracked these grants through an internally developed software application beginning with grants funded in FY2015 (one year prior to the policy effective date). The NIMH also funds basic behavioral researcher. Basic behavioral researchers were among the forefront of those who expressed concerns with the potential burdens of the revised

definition on their research (FABBS, 2017). Therefore, the impact of the revised clinical trial definition implementation on the progress of NIMH-funded grants can be used to forecast the potential impact across NIH.

Methods

Study Overview

This quasi-experimental study uses a difference-in-differences design to evaluate the effect of the revised NIH clinical trial definition policy on research participant recruitment progress in NIMH-funded clinical trial grants from FY2015-2017. This study examines the difference in effect before and after the policy implementation for clinical trial grants that would have been defined by NIMH as clinical trials both before and after the new policy was implemented (control group) versus a set of studies that would not have been deemed clinical trials in the pre-policy period but were identified as clinical trials under the new policy (intervention group). The revised clinical trial definition policy became effective beginning with FY2016 grants (NIH, 2014); therefore, this study compares the difference in recruitment progress for clinical trials initially funded from FY2015-2017, with grants funded in FY2015 not subject to the new clinical trial definition policy and grants funded in FY2016 and FY2017 subject to the policy. The primary outcome is a binary measure of whether or not the 20-month recruitment milestone was met. The overall hypothesis is that this policy is not harmful to recruitment progress; therefore this study will test the null hypothesis that the revised clinical trial definition policy will have no effect on the difference-in-differences for recruitment progress before and after the policy took effect in a group of studies newly identified as clinical trials under the policy relative to a comparison group of clinical trials unaffected by the new policy. Recruitment progress delays would be demonstrated by a significant worsening ($p<0.05$) in the difference-in-differences between the two arms after policy implementation.

Study Sample

The study sample was comprised of grants that met the following eligibility criteria: (1) new competing applications and competing renewals (i.e., applications seeking new years of funding for new aims) for non-fellowship; (2) non-HIV/AIDS research grants; (3) awarded by NIMH from FY2015-2017; (4) NIH-defined clinical trials (using the revised definition); and (5) with recruitment progress data available in the NIMH Recruitment Milestone Reporting database. "Delayed onset" trials (i.e., trials that do not begin until year 2-3 of a grant by intentional design) were excluded because they would not have comparable recruitment progress data.

Clinical trial grants were allocated to the control arm if the funding application was submitted and funded through a NIMH Clinical Trial Funding Opportunity Announcement (FOA). The NIMH Clinical Trial FOAs outlined the types of clinical trials accepted by NIMH through the experimental therapeutics paradigm established prior to the implementation of the revised policy (Insel & Gogtay, 2014; NIMH, n.d.). These announcements were exclusively reserved for trials designed to "establish the safety, clinical efficacy, effectiveness, clinical management and/or implementation of preventive, therapeutic, or therapeutic interventions." These FOAs were mandatory for any trial design toward those goals. These trials were included in the control arm because they would have been deemed clinical trials before and after the new clinical trial definition policy went into effect in FY2016; the policy did not affect this sub-set of trials.

The intervention group consists of all clinical trials funded by NIMH in FY2015-17 that were (or would have been) considered a clinical trial under the revised definition but were not counted under the previous definition. Non-traditional clinical trials, such as mechanistic trials and BESH trials, are not accepted under the NIMH clinical trial funding announcements because they do not follow the experimental therapeutics approach. Clinical trial grants that were not submitted under the NIMH Clinical Trial FOAs were allocated to the intervention arm; this subset of trials would not have been

deemed clinical trials in the pre-policy period but were defined as clinical trials under the new policy. The intervention arm also captures "traditional" clinical trials that should have been submitted through the NIMH Clinical Trial FOAs but were not identified or peer-reviewed as clinical trials under the old definition.

Measures

The dependent variable in this analysis was recruitment performance. Acceptable recruitment performance was defined by the actual recruitment progress meeting or exceeding the target recruitment at the fifth triannual reporting window (approximately 20 months). Sensitivity analyses were conducted using varying thresholds to define acceptable recruitment progress (i.e., 95%, 90%, and 80% of target). The independent variable was the NIH clinical trial definition policy. Potential confounders controlled for in the analyses were initial fiscal year of funding, NIMH funding division, total grant funds requested, ClinicalTrials.gov registration, planned trial sample size, and total amount of NIH funding to the grantee institution.

Data Collection

Sample Identification and Abstraction

Clinical trial grants were identified from the NIMH Clinical Trial Operations Software database. The NIMH Clinical Trial Operations Software database was queried for all studies meeting the intervention and control group criteria described above and initially funded FY2015-2017. This was possible because the NIMH had previously identified and recorded the FY2015 (pre-policy change) grants that would have been deemed clinical trials under the new definition.

Figure 1 illustrates the sample selection process. The 296 non-HIV/AIDS NIMH-funded grants were downloaded to a Microsoft Excel spreadsheet. HIV/AIDS grants were excluded because the NIMH

was considering a reorganization of these programs at that time and the relevant data were therefore not collected. The initial fiscal year of funding and NIMH funding division for each grant were also abstracted from this system. The results were manually cross-referenced with the NIMH Recruitment Milestone Reporting database to identify which clinical trials had triannual recruitment reporting data. 164 grants did not report triannual recruitment data or did not have recruitment reporting data available at the 20-month timepoint and were excluded from this analysis. Possible reasons for the absence of recruitment data in the NIMH Recruitment Milestone Reporting database include planned delayed onset trials (trial not scheduled to begin in the first grant year) and smaller grants (reporting was not mandatory for clinical trials with sample sizes of less than 150 participants prior to FY2017). The remaining 132 studies comprised the sample for this study. The grant applications for these studies were reviewed in the NIH IMPAC II database to identify the funding opportunity announcement to which the grant application was submitted. Applications submitted to a NIMH Clinical Trial FOA were allocated to the control arm. Grant applications that met the revised NIH clinical trial definition but were submitted to any non-clinical trial FOA were allocated to the intervention arm.

Outcome Identification and Abstraction

The NIMH Recruitment Milestone Reporting database was queried for recruitment data for each study. The original recruitment milestone target and actual reported recruitment numbers were recorded for the fifth triannual reporting window (approximately 20 months from recruitment initiation). These data were used to determine whether the study was meeting recruitment goals at 20 months.

Covariate Identification and Abstraction

As previously noted, the initial fiscal year of funding and NIMH funding division were abstracted as categorical variables from the Clinical Trial Operations Software database during the clinical trial sample abstraction. The initial fiscal year of funding was used to identify the applicability of the clinical trial definition policy ("Policy Intervention"). The policy did not apply to FY2015 grants and did apply to FY2016 and FY2017 grants. Using the NIH IMPAC II database, each grant was manually reviewed to abstract the total funding requested, the grantee institution name, and whether the study was registered in ClinicalTrials.gov ("ClinicalTrials.gov Registration"). Grantee Institution Size was determined by manually cross-referencing the grantee institution name with the total NIH funding in FY2016 identified in the NIH Research portfolio Online Reporting Tool (https://report.nih.gov/award/index.cfm) and coded as an ordinal categorical variable (in increments of $100M USD in FY16). The Planned Trial Sample Size was abstracted from the NIMH Recruitment Milestone Reporting database by searching for each clinical trial grant number.

Analysis

Sample characteristics were analyzed by group (intervention and control). The associations between covariates and group were analyzed using Fisher's exact test and the Student's t-tests. Two multiple logistic regressions were performed to examine the effect of the policy on recruitment progress for each group. Then, a multiple logistic regression calculating the difference in pre/post policy change in recruitment progress in the intervention versus control groups (the difference-in-differences) was conducted via the following model:

$$Y = \beta_0 + \beta_1*[\text{Group}] + \beta_2*[\text{Policy Intervention}] + \beta_3*[\text{Difference-in-Differences}] + \beta_4*[\text{Fiscal Year}] + \beta_5*[\text{NIMH Division}] + \beta_6*[\text{Total Grant Funds Requested}] + \beta_7*[\text{ClinicalTrials.gov Registered}] + \beta_8*[\text{Planned Trial Sample Size}] + \beta_9*[\text{Grantee Institution Size}] + \varepsilon$$

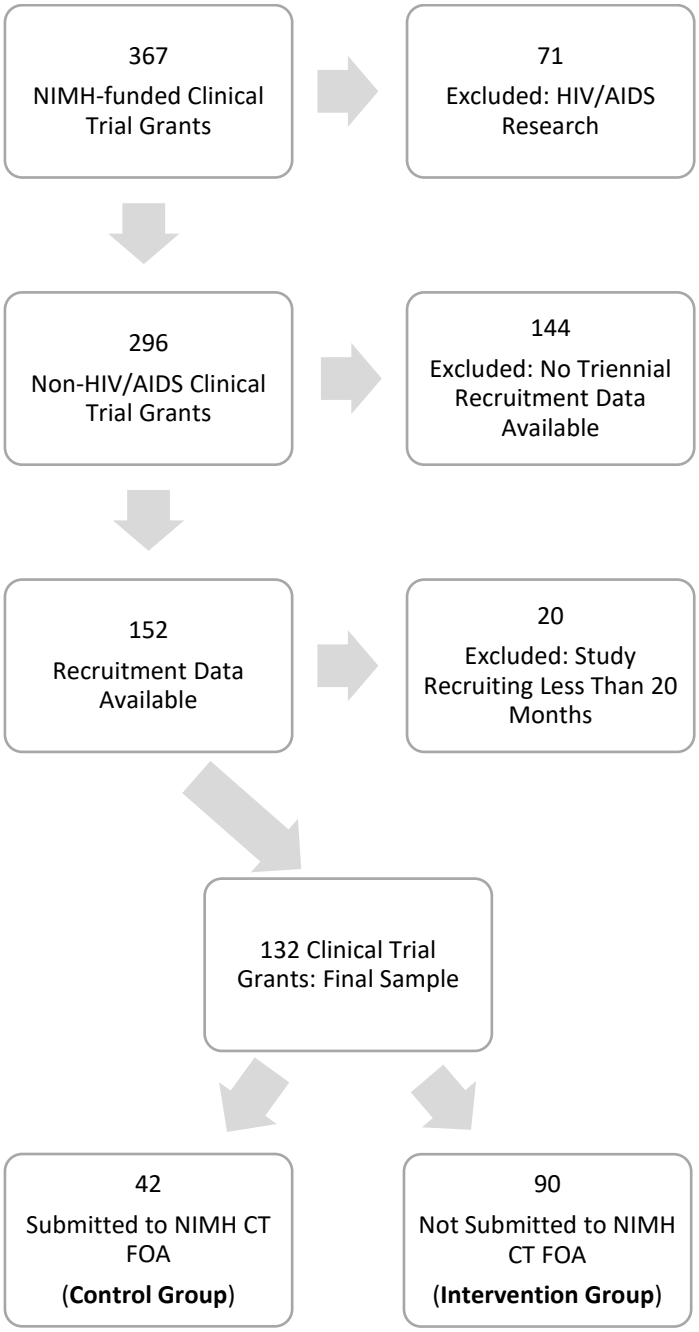
The Difference-in-Differences variable was calculated using Group*Policy Intervention; therefore, the coefficient for this variable represents only those grants that were reclassified by the definition change after the policy went into effect. The model fit was validated using Pearson's goodness-of-fit test (p=0.244) and the Hosmer-Lemeshow statistic (p=0.596) which did not indicate that the predicted probabilities deviate from the observed probabilities in a way that the binomial distribution does not predict (Minitab, 2019). These analyses were conducted using Stata/IC Version 14.2 (StataCorp, 2015).

Results

From 2015-2017, the NIMH funded 367 grants that met the new NIH definition of clinical trial. 296 of these were non-HIV/AIDS research. 144 of these trials did not have recruitment data available in the NIMH Recruitment Milestone Reporting system. The primary reason for data not being available is that the NIMH Recruitment Milestone Reporting system only captured trials with a planned sample size of greater than 150 participants before FY2017. 119 (83%) of these excluded grants were funded in FY2015 and FY2016 prior to that change. Fellowship awards comprised an additional 10 (6.9%) of these excluded grants. Fellowships were exempt and can no longer contain clinical trials under NIH policy. Many of the excluded grants were also designed as shorter length grants, such as an R03 mechanism, with 48 (33.3%) having 2 years or less years of funding and 70 (48.6%) having three years or less. Of the 144 grants that did not report recruitment data, 18 (12.5%) were funded by the Division of Neuroscience and Basic Behavioral Science, 89 (61.8%) by the Division of Translational Research, 29 (20.1%) by the Division of Services and Intervention Research, and 8 (5.5%) by the Office of the NIMH Director.

Of the remaining 152 trials, 20 were excluded because recruitment had not (or would not) reach the fifth triannual recruitment window. Reasons for not reaching the window included delayed-onset trials or early closure of the grant. No instances of early closure were observed as resulting from insufficient recruitment. The remaining 132 clinical trial grants constituted the sample for this analysis.

Figure 1: Sample Selection



Sample Demographics

The sample demographics and statistical association between covariates are displayed by group in Table 1. In total, 42 grant applications were in the control group and 90 were in the intervention group. In the control group, 36% of trials were meeting or exceeding recruitment goals while 43% were meeting or exceeding recruitment goals in the intervention group. Of the 90 grants in the intervention group, 38 were funded in FY2015 prior to the definition change while 52 were funded in FY2016-2017 after the policy was effective. The association between initial fiscal year of funding and group was statistically significant. The average funding requested was nearly equal between groups while the average planned sample size was notably lower for the intervention group. Neither of these associations were statistically significant. The majority of clinical trials were funded through the NIMH's Division of Services and Intervention Research and the Division of Translational Research. The association between funding division and group was statistically significant. The R01 funding mechanism was the most frequently used funding mechanism for both groups. The rate of ClinicalTrials.gov registration was comparatively 66% higher in the control group relative to the intervention group and the association was statistically significant. Of the 52 grants funded in FY2016-17 that were considered clinical trials due to this policy, 69% have registered in ClinicalTrials.gov. Clear differences were observed based upon the type of clinical trial. Only 12.5% (1) of the basic science studies considered clinical trials due to this policy clinical trials were registered while 55% (6) of mechanistic clinical trials and 85% (27) of randomized clinical trials were registered. The association between funding mechanism and group was statistically significant. The association between intervention type and group was statistically significant. The association between grantee institution size and group was not statistically significant.

Table 1. Sample Demographics by Group (percents are column percents)

	Control Group	Intervention Group	p-value
n (%)	42	90	
Initial Fiscal Year of Funding			**0.045**
2015	10 (23.8%)	38 (42.2%)	
2016	6 (14.3%)	17 (18.9%)	
2017	26 (61.9%)	35 (38.9%)	
Average Total Requested Funding	$ 2,739,379	$ 2,732,130	0.065
Funding Division			**0.020**
Office of the NIMH Director	0 (0%)	4 (4.4%)	
Division of Neuroscience and Basic Behavioral Science	0 (0%)	3 (3.3%)	
Division of Services and Intervention Research	23 (54.8%)	26 (28.9%)	
Division of Translational Research	19 (45.2%)	57 (63.3%)	
Funding Mechanism			**<0.001**
Career Development Awards (K)	0 (0%)	8 (8.9%)	
Program Project Grants/Center Grants (P)	0 (0%)	3 (3.3%)	
Cooperative Agreements (U)	1 (2.4%)	4 (4.4%)	
R01	18 (42.9%)	58 (64.4%)	
R34	8 (19.0%)	3 (3.3%)	
R61/R33	12 (28.6%)	0 (0%)	
Other Research Grants (R)	3 (7.1%)	14 (15.6%)	
Average Planned Trial Sample Size	605	355	0.326
Design Type			**<0.001**
Basic Science Clinical Trial	0 (0%)	20 (22.2%)	
Group Randomized Controlled Trial	2	2 (2.2%)	
Mechanistic Clinical Trial	0 (0%)	26 (28.9%)	
Individually Randomized Controlled Trial	39	36 (40.0%)	
Other	1	6 (6.7%)	
Intervention Type			**<0.01**
Behavioral	31 (73.8%)	39 (43.3%)	
Device	6 (14.3%)	19 (21.1%)	
Drug	5 (11.9%)	14 (15.6%)	
Surgical	0 (0%)	1 (1.1%)	
Other	0 (0%)	17 (18.9%)	
ClinicalTrials.gov Registration Reported to NIMH	90.5%	54.4%	**<0.001**
Grantee Institution Size (in FY2016 NIH Funding)			0.678
X <$100,000,000 USD	13 (31.0%)	38 (42.2%)	
$100,000,000 ≤ X < $200,000,000	12 (28.6%)	18 (20.0%)	
$200,000,000 ≤ X < $300,000,000	5 (11.9%)	8 (8.9%)	
$300,000,000 ≤ X < $400,000,000	2 (4.8%)	4 (4.4%)	
$400,000,000 < X	10 (23.8%)	22 (24.4%)	

Regression Analyses

Multiple logistic regressions were performed to identify the association between the policy and recruitment performance for each group. As shown in Table 2, the multiple logistic regression model (p=0.52) for the control group did not find a significant association between the policy and on-target recruitment progress with an odds ratio of 2.44 [p=0.70; 95% CI: 0.03, 227.71]. Similarly, as shown in Table 3, the multiple logistic regression model (p<0.001) for the intervention group did not find a statistically significant association between the policy and on-target recruitment progress with an odds ratio of 4.05 [p=0.33; 95% CI: 0.24, 68.42].

Table 2. Odds of On-Target Recruitment Progress at 20 Months in Control Group

	Odds Ratio	Standard Error	z	P>|z|	[95% Confidence Interval]	
Policy Intervention	2.44	5.65	0.39	0.70	0.03	227.71
Initial Fiscal Year of Funding	0.46	0.56	-0.64	0.53	0.04	5.11
NIMH Division						
Division of Translational Research	REF	REF	REF	REF	REF	REF
Division of Services and Intervention Research	0.79	0.62	-0.31	0.76	0.17	3.66
Total Grant Funds Requested	1.00	0.01	0.15	0.88	0.98	1.03
ClinicalTrials.gov Registered	1.10	1.66	0.07	0.95	0.06	21.02
Planned Trial Sample Size	1.00	0.00	-0.62	0.54	1.00	1.00
Grantee Institution Size						
X <$100,000,000 USD						
$100,000,000 ≤ X < $200,000,000	7.07	7.43	1.86	0.06	0.90	55.52
$200,000,000 ≤ X < $300,000,000	1.00	-	-	-	-	-
$300,000,000 ≤ X < $400,000,000	6.69	11.47	1.11	0.27	0.23	193.04
$400,000,000 < X	8.60	9.46	1.96	0.05	1.00	74.28

Table 3. Odds of On-Target Recruitment Progress at 20 Months in Intervention Group

	Odds Ratio	Standard Error	z	P>|z|	[95% Confidence Interval]	
Policy Intervention	4.05	5.84	0.97	0.33	0.24	68.42
Initial Fiscal Year of Funding	0.17	0.14	-2.11	0.04	0.03	0.88
NIMH Division						
Division of Translational Research	REF	REF	REF	REF	REF	REF
Office of the NIMH Director	1.07	1.28	0.05	0.96	0.10	11.13
Division of Neuroscience and Basic Behavioral Science	4.26	6.60	0.94	0.35	0.20	88.78
Division of Services and Intervention Research	0.83	0.62	-0.25	0.81	0.19	3.58
Total Grant Funds Requested	0.99	0.01	-0.84	0.40	0.98	1.01
ClinicalTrials.gov Registered	0.47	0.32	-1.09	0.28	0.12	1.81
Planned Trial Sample Size	1.00	0.00	-1.96	0.05	0.99	1.00
Grantee Institution Size						
X <$100,000,000 USD	REF	REF	REF	REF	REF	REF
$100,000,000 ≤ X < $200,000,000	0.35	0.27	-1.36	0.17	0.08	1.59
$200,000,000 ≤ X < $300,000,000	0.49	0.48	-0.74	0.46	0.07	3.30
$300,000,000 ≤ X < $400,000,000	5.09	6.67	1.24	0.22	0.39	66.42
$400,000,000 < X	4.48	3.25	2.07	0.04	1.08	18.59

To examine the effect of the clinical trial definition policy on the recruitment progress outcome in the intervention group relative to the control group, a difference-in-differences multiple logistic regression was performed. The results of this difference-in-differences analysis are displayed in Table 4. This multiple logistic regression model has a chi-squared probability <0.01 and explains 19.9% of the variance (R^2). The difference-in-differences between the grants affected by the policy intervention and the control grants not affected by the intervention did not show statistically significant worsening in recruitment progress. The results of sensitivity analyses using alternate measures of recruitment success were consistent with main findings. Reducing the "success" threshold from 100% actual-to-target to 95%, 90%, and 80% accordingly did not alter the findings. Only the grantee institution size (specifically those institutions receiving at least $400,000,000 in FY2016 NIH funding) was associated with a statistically significant increase in odds of meeting recruitment performance milestones.

Table 4. Difference-in-Differences for Odds of On-Target Recruitment Progress at 20 Months

	Odds Ratio	Standard Error	z	P>|z|	[95% Confidence Interval]	
Difference-in-Differences (Policy Effect)[1]	0.393	0.427	-0.860	0.390	0.047	3.306
Non-NIMH Clinical Trial FOA[2]	1.465	1.396	0.400	0.688	0.226	9.486
Policy Intervention[3]	4.865	6.881	1.120	0.263	0.304	77.787
Initial Fiscal Year of Funding	0.324	0.207	-1.770	0.077	0.093	1.130
NIMH Division						
Division of Translational Research	REF	REF	REF	REF	REF	REF
Office of the NIMH Director	0.786	0.883	-0.210	0.830	0.087	7.103
Division of Neuroscience and Basic Behavioral Science	2.225	3.190	0.560	0.577	0.134	36.976
Division of Services and Intervention Research	0.735	0.374	-0.600	0.546	0.271	1.994
Total Grant Funds Requested	0.995	0.006	-0.860	0.390	0.983	1.007
ClinicalTrials.gov Registration Reported to NIMH	0.532	0.288	-1.160	0.244	0.184	1.538
Planned Trial Sample Size	0.999	0.001	-1.360	0.175	0.996	1.001
Grantee Institution Size[4]						
X <$100,000,000 USD						
$100,000,000 ≤ X < $200,000,000	1.163	0.649	0.270	0.787	0.389	3.474
$200,000,000 ≤ X < $300,000,000	0.506	0.406	-0.850	0.396	0.105	2.443
$300,000,000 ≤ X < $400,000,000	5.184	5.134	1.660	0.097	0.744	36.120
$400,000,000 ≤ X	4.946	2.801	2.820	**0.005***	1.630	15.009

[1]Difference-in-Differences for applications changed by policy implementation; [2]X=1 if grant application was not submitted to NIMH Clinical Trial FOA; [3]Revised NIH Clinical Trial Definition;
[4]Categorical variable increasing in blocks of $100,000,000 FY2016 NIH funding
*Significant at the p<0.01 level

Discussion

Some researchers and professional groups expressed strong concerns that the revised NIH clinical trials definition would overwhelm the newly-identified clinical trials with administrative requirements that would delay the research. Study results do not support the claim that the revised clinical trial definition impeded achievement of recruitment targets. These results suggest that the revised policy had no effect on recruitment progress. This analysis of NIMH-funded clinical trials can be used by both the NIMH and the NIH when engaging affected stakeholders to discuss the impact of this policy.

Recruitment progress is a relevant outcome measure for monitoring potential delays in research study progress, but it does not represent all implications associated with the revised clinical trial definition policy. This study focused exclusively on potential recruitment delays. The study did not

evaluate associated factors such as researcher stress/burnout, measures of research productivity such as the relative citation ratio, or the benefits of increased ClinicalTrials.gov registration and results sharing from a larger pool of clinical trials. These factors should be examined in future research.

Interestingly, one factor that was significantly associated with a positive increase in odds of on-target recruitment progress was the size of the grantee institution's total NIH funding. Specifically, the recipients of very large sums of NIH funding had much higher odds of on-target recruitment performance. Meanwhile, the amount of funding within a single grant or trial did not appear to have the same effect. While this study was not designed to make inferences on the value of individual versus total institution funding, it does raise an interesting question for future research. Does the total NIH funding influence a grantee institution's ability to recruit across all studies and "lift all boats"?

This study has a number of limitations. First, the recruitment progress ratio data (dependent variable) were analyzed and determined to be non-normally distributed by histogram, Shapiro-Wilk test, and Q-Q plot and remained non-normally distributed (low kurtosis) after log-transformation. The non-normal distribution of recruitment progress ratios necessitated compression of a continuous variable into a binary variable. Second, only one year of pre-intervention data was available, which does not allow for establishing extended pre-intervention trends in recruitment progress in the intervention and control arms. Third, as shown in Table 1 and as discussed in the Introduction, the "traditional" clinical trials in the control arm are different in nature from the non-traditional clinical trials in the intervention arm; in other words, the control arm is not a perfect counterfactual (or an "apples to apples" comparison) with the intervention arm. Fourth, this study did not account for historically high/low performing researchers/research teams; density of research participants in a geographic area; or different diseases, disorders, or health conditions. Fifth, this design examined funded grants and did not address potential barriers to funding resulting from the policy change. Finally, the analysis sample was limited by the records available in the NIMH Recruitment Milestone Reporting database, which did not

capture smaller trials (n<150) prior to FY2017. The small sample size limited the power of this study to detect an effect. At 80% power, this analysis could only detect an effect greater than a 25% change in odds of meeting recruitment progress milestones.

Conclusions

Numerous NIMH-funded grants that were not classified as clinical trials under the old definition were identified as clinical trials under the revised definition. Many of these grants were basic science or mechanistic clinical trials. Although these newly-classified clinical trials were subject to a range of NIH clinical trial policies due to the revised NIH clinical trial definition, this study did not find a negative effect on recruitment progress as compared to traditional clinical trials. Concerns regarding administrative delays and burden impacting study progress may be alleviated by these initial results. Further research is needed to establish longer before/after trendlines with a larger sample to power detection of smaller effect sizes.

References:

APS. (2017, June 6, 2017). Re: Clarification of NIH Clinical Trial Policy. Retrieved from https://fabbs.org/wp-content/uploads/2017/10/APS-to-Dr.-Collins-re-clinical-trials-policy-6-6-17.pdf

APS. (2018). Make Your Voice Heard: Tell NIH You Oppose the Classification of Basic Human Subjects Research as Clinical Trials. Retrieved from https://www.psychologicalscience.org/policy/make-your-voice-heard-tell-nih-you-oppose-the-classification-of-basic-human-subjects-research-as-clinical-trials.html

DHHS. (2017). Federal Policy for the Protection of Human Subjects ('Common Rule'). *45 CFR 46.* Retrieved from https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html

FABBS. (2017, July 12, 2017). Letter to NIH-Collins Re Clinical Trials. Retrieved from https://fabbs.org/wp-content/uploads/2017/08/Letter-to-NIH-Collins-Re-Clinical-Trials-FINAL.pdf

Hudson, K. L., Lauer, M. S., & Collins, F. S. (2016). Toward a New Era of Trust and Transparency in Clinical Trials. *Jama, 316*(13), 1353-1354. doi:10.1001/jama.2016.14668

ICMJE. (n.d.). Clinical Trials Registration. Retrieved from http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/

Insel, T. R., & Gogtay, N. (2014). National Institute of Mental Health clinical trials: new opportunities, new expectations. *JAMA Psychiatry, 71*(7), 745-746. doi:10.1001/jamapsychiatry.2014.426

Kaiser, J. (2017, July 18, 2017). Some scientists hate NIH's new definition of a clinical trial. Here's why. *Science*. Retrieved from http://www.sciencemag.org/news/2017/07/some-scientists-hate-nih-s-new-definition-clinical-trial-heres-why

Minitab, L. (2019). Goodness-of-fit tests for Simple Binary Logistic Regression. Retrieved from which illustrates predicted probabilities do not deviate from the observed probabilities in a way that the binomial distribution does not predict,

NIH. (2014). Notice of Revised NIH Definition of "Clinical Trial". *NOT-OD-15-015.* Retrieved from https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html

NIH. (2016). NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information. *NOT-OD-16-149.* NOT-OD-16-149.

NIMH. (n.d.). Support for Clinical Trials at NIMH. Retrieved from https://www.nimh.nih.gov/funding/opportunities-announcements/clinical-trials-foas/index.shtml#part_156836

Reif-Lehrer, L. (2005). *Grant Application Writer's Handbook* (4th Edition ed.): Jones & Bartlett Learning.

StataCorp. (2015). Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.

WHO, W. H. O. (n.d.). International Clinical Trials Registry Platform (ICTRP). Retrieved from https://www.who.int/ictrp/en/

Integration and Policy Implications

The first aim of this dissertation identified the new and revised NIH and NIMH clinical trial policies from 2005-2019 and summarized the potential benefits and potential burdens of those policies. Five new/revised NIH-wide and four NIMH-only clinical trial policies were identified. The five NIH-wide clinical trial policies (1) required planning for post-trial access to antiretroviral treatments; (2) revised the clinical trial definition; (3) implemented clinical trial-specific funding opportunity announcements (FOA), peer-review criteria, progress reporting; (4) mandated good clinical practice (GCP) training; and (5) expanded ClinicalTrials.gov registration and results reporting requirements to all NIH-funded trials. The four NIMH-specific clinical trial policies (1) implemented clinical trial-specific FOAs, peer-review criteria, progress reporting; (2) established data and safety monitoring requirements; (3) defined expectations for oversight by data and safety monitoring boards and independent safety monitors; and (4) expanded recruitment progress monitoring and reporting to clinical trials of all sizes.

Aim 1 also illustrated the perceived benefits and burdens of those clinical trial policies. Potential benefits were the improved identification, review, conduct, and reporting of publicly-funded clinical trials. Potential burdens were loss of researcher time, potential loss of future research funding opportunities for basic behavioral researchers, and widespread confusion (for both researchers and the general public) resulting from an overlap between clinical trials and basic science.

NIH developed and implemented these policies to build structure for NIH-funded grants with the intent of influencing subsequent processes and outcomes. Despite this goal, neither the NIH nor the NIMH incorporated clear outcome evaluation into these policies. Without planned evaluation outcomes and methods, the NIH and NIMH would struggle to demonstrate that the policies have successfully achieved their objectives of improving clinical trials. Similarly, the NIH and NIMH would have difficulty

responding to public concerns that the burdens of compliance outweigh the benefits of the policies. The second and third aims of this dissertation attempted to partially address this gap by evaluating the impact of two of these clinical trial policies recruitment performance and relative citation ratio outcomes.

In Aim 2, the impact of the NIH's clinical trial recruitment policy on mean and maximum relative citation ratios was examined by evaluating a similar NIMH-specific recruitment policy that was implemented years earlier. The implementation of the policy was associated with an increased mean relative citation ratio, which suggests that the NIH-wide recruitment monitoring policy may also be associated with an increased mean relative citation ratio. While more research is needed to examine the specific effects of the NIH-wide policy, these results suggest that the benefits of this policy on the relative citation ratio may outweigh the compliance burden.

In Aim 3, the impact of the revised NIH clinical trial definition on study participant recruitment progress was examined by evaluating the impact on NIMH-funded grants. NIMH-funded grants were chosen because the NIMH began identifying and tracking trials that would have met the revised definition prior to the policy effective date. The NIMH grants were also inclusive of the types of research (i.e., basic behavioral and social sciences) that raised potential burden concerns in Aim 1. To identify whether the policy led to administrative delays in research, the difference-in-differences for odds of on-target recruitment progress was examined in NIMH-funded traditional clinical trials versus NIMH-funded clinical trials that were newly-identified by the revised policy. While the study had limitations, the results did not indicate that the burden of compliance negatively impacted study progress.

Cross-cutting Themes and Implications

Several cross-cutting themes emerged during this dissertation. First, the NIH and NIMH should prioritize stakeholder engagement and communication early during policy development. Without stakeholder engagement during the policy development, it is likely that certain perspectives, including unique perceived burdens, will be underrepresented. This can limit policy acceptance/adherence and reduce the effectiveness of burden minimization. Once this opportunity has been missed, the policy maker's time and effort are then redirected to addressing these challenges after the fact. This was observed across numerous NIH clinical trial policies.

Second, a thorough examination of the rationale, potential benefits, and potential burdens should be incorporated into policy development. Policy makers need to clearly articulate the need and rationale for a new or revised policy. This rationale should be weighed against the balance of potential benefits and potential burdens and should be carefully considered to maximize the benefits and minimize or mitigate the burdens. The majority of NIH and NIMH clinical trial policies examined in this research did not formally solicit feedback from external stakeholders during the development stage.

Third, while the post-hoc examination of the specific policies in Aims 2 and 3 demonstrated positive and neutral outcomes respectively, this may not be the case for all policies or for other outcomes of related to these policies. Policy development must include a priori identification of relevant outcomes and a formal plan to evaluate those outcomes. These outcomes should include both the primary focus of the policy as well as metrics to monitor potential burdens. Without outcome evaluation, it is impossible to measure the impact of the potential benefits or potential burdens. This logically leads to an inability to determine whether the policy is a success or a failure. NIH and NIMH need this information when engaging a range of stakeholders including not just the research community but also extending to the patient community and congress when justifying stewardship over public funds.

Need for Future Research

The findings of this dissertation do not call for immediate changes to the suite of clinical trial policies that have been developed by the NIH and NIMH. However, this research does illustrate the need for improvement in future policy development through increased stakeholder engagement, evaluation design, and dissemination. This dissertation is the first systematic evaluation of the impact of NIH and NIMH clinical trial policies, but these analyses were designed post-hoc and limited to research funded by NIMH. Further research and evaluation are needed to continue this investigation. Future research should include broader ranges of science (diseases and disciplines beyond just mental health) to be more representative of the NIH research community. These studies should establish and evaluate better grant performance outcome measures that bridge the gap from research scholarship into changes in clinical practice. Finally, future studies should capture larger samples of research grants and consider additional covariates such as the effect of disease prevalence within geographic regions on recruitment potential.

Curriculum Vitae

Eugene Ignatius Kane III

Eugene.Kane.3@gmail.com

7620 Old Georgetown Road
Apartment 330
Bethesda, Maryland 20814
c: 240-731-8570

EDUCATION

Johns Hopkins University — Baltimore, MD
Johns Hopkins Bloomberg School of Public Health
Doctor of Public Health — 2020 (Anticipated)
Healthcare Leadership and Management Concentration
GPA: 4.0

Johns Hopkins University — Baltimore, MD
Johns Hopkins Bloomberg School of Public Health
Master of Public Health — 2014
GPA: 3.93

Boston College — Chestnut Hill, MA
College of Arts and Sciences
Bachelor of Science — 2008
Major: Biochemistry, Pre-Medical Concentration

PROFESSIONAL EXPERIENCE AND ACCOMPLISHMENTS

Office of Clinical Research — Bethesda, MD
National Institutes of Health/National Institute of Mental Health (NIMH)
Deputy Chief, Human Research Protection Branch [*GS-0601-14***]** — **2016-Present**
Public Health Advisor [*GS-0601-11/12/13***]** — **2012 – 2016**
Contractor — **2011 – 2012**

Senior Advisor for Human Research Protection and Regulatory Compliance:

- Advise the National Institute of Mental Health (NIMH) Director, Deputy Director, and Director of Clinical Research on policy matters and concerns related to human subject protection and regulatory compliance.
- Develop policies, procedures, and systems to ensure oversight and management of human subject research protection at the NIMH.
- Serve as NIMH representative on numerous NIH-wide committees and working groups.
- Serve as the Institutional Review Board (IRB) expert for the NIMH.
- Interpret regulations and guidance from various federal agencies as related to research projects and programs.
- Provide scientific, regulatory, and ethical guidance to the NIMH OD, program staff, clinical staff, and NIMH funding recipients.
- Design and analyze reports regarding clinical research ethics, data and safety monitoring, informed consent, and human subject protections.
- Conduct “for-cause” clinical research audits and site visits.

- Coordinate with NIH, NIMH Program, grant applicants, and institutional officials to revise grant application to resolve restrictions to grant funding on the basis of human subject protection concerns (code 48).
- Design, develop, and implement Clinical Trial Operations Software (CTOS) application to oversee appropriate data and safety monitoring across all NIMH-funded clinical trials.
- Serve as conflict of interest regulatory expert for the NIMH.
- Hire/train human research protection specialists.
- Manage Office of Clinical Research budget and operations.
- Supervise office contractor staff.
- Director of human research protection education program.

Data and Safety Monitoring Board (DSMB) Scientific Administrator:

- Serve as Executive Secretary for NIMH-constituted DSMBs and serve as a Data and Safety Monitoring expert.
- Provide regulatory guidance to the NIMH DSMBs and ensure fair and comprehensive review of clinical trials.
- Identify scientific, technical, bioethical, or regulatory issues in trials under NIMH DSMB review.
- Independently execute special studies and analyses of issues of significant interest to the DSMB and NIMH Director.
- Responsible for official correspondence between the NIMH DSMB and NIH staff, grantees, and Institutional Review Boards.

Certificates of Confidentiality (COC) Coordinator and Program Manager (2011-2018):

- Reviewed all COC applications, IRB correspondence, and informed consent documents to determine eligibility based on adequacy of human subject protection, justification for use, and institutional assurances that the certificate protections will be executed by applicants as promised to research participants.
- Engaged and educated federal and non-federal investigators, applicants, institutional officials, IRB Chairpersons, and other interested parties (government, academia and industry) about the privacy protections offered by Certificates of Confidentiality as well as the associated individual and institutional responsibilities.
- Managed COC program staff and resources.

Dana-Farber Cancer Institute (DFCI)
Office for Human Research Studies (OHRS) Boston, MA
Human Research Coordinator II **2010 –2011**
Human Research Coordinator I **2008 –2010**

Institutional Review Board (IRB) Member:

- Served as Dana-Farber Cancer Institute (DFCI) IRB Member by reviewing new protocol submissions, amendments to previously approved research, and annual reviews for human research studies conducted at the Dana-Farber/Harvard Cancer Center (DF/HCC).
- Served as Data and Safety Monitoring Committee liaison to the IRB and the OHRS by facilitating communication and cooperation between governing boards regarding patient safety and the management of clinical trials.
- Served as Conflict of Interest liaison to the IRB and the OHRS by negotiating oversight of financial and intellectual conflict of interest management plans between the IRB and various DF/HCC institutional conflict of interest offices.

Senior Clinical Trial Regulatory Coordinator:

- Served on a research oversight committee to review requests to reinstate research privileges at the Beth Israel Deaconess Medical Center.
- Interpreted regulations and guidance from various federal agencies as related to research projects and programs.
- Provided regulatory and ethical guidance and training to investigators, clinical staff, and research coordinators from local and regional hospitals and non-profits.
- Advised and educated senior Investigators, Clinicians, and Leadership at the King Faisal Specialist Hospital and Research Center (Riyadh, Saudi Arabia) on research ethics and U.S. human subject research regulations in order to dramatically expand and enhance the institution's research portfolio.
- Managed team of IRB coordinators responsible for a portfolio of clinical research trials spanning numerous disease programs and established acceptable review timelines for the team and reported to senior leadership.
- Successfully prepared the DF/HCC for a National Cancer Institute Comprehensive Cancer Center Support Grant 5-year renewal process in coordination with DFCI senior leadership.
- Designed, performed, and managed a multi-institutional audit of new protocol review performance metrics from 2005 to 2011 with a staff of over 20 coordinators reviewing approximately 2000 clinical research studies.
- Designed and implemented a paperless review process within the Office for Human Research Studies saving administrative resources and time while benefitting the environment.
- Designed and tested a new multi-institutional clinical trials management system to ensure that it complemented the current policies, procedures, and federal regulations as well as future development plans at OHRS.
- Mentored Interns through the DFCI OHRS-Northeastern University Master of Science in Regulatory Affairs Internship Program.
- Independently designed and managed a project to create and maintain a standard lay language database for drug/procedure risks, thereby reducing the time that investigators spend writing/editing the consent documents and reducing the time required for thorough IRB review.
- Interviewed candidates for employment at OHRS and made recommendations to the OHRS Senior Director.
- Expertise and skill in planning, organizing, and coordinating activities associated with conferences, workshops, meetings, and other activities.

Boston College Information Technology Services (BC ITS) Chestnut Hill, MA
ResNet Student Program Coordinator **2007-2008**
ResNet Student Technology Specialist **2005-2007**

- Managed a staff of 80 student employees across 5 university departments.
- Interviewed, hired, and trained over 40 new student employees during my time as Program Coordinator.
- Designed and delivered multiple IT education programs to students and employees
- Maintained employee scheduling logistics for various campus initiatives and events.
- Coordinated with ITS department managers to establish program-wide standards and maintenance by directing monthly meetings and quarterly performance reviews.

CVS/Pharmacy Montgomery Village, MD
Certified Pharmacy Technician **2006**

- Extensively trained in HIPAA Confidentiality Standards and applied these principles to the front lines of healthcare.
- Filled prescriptions, billed insurance companies, and resolved disputes on behalf of customers.

HONORS OR AWARDS

- Eagle Scout; Boy Scouts of America (2003)
- NIH Director's Award (2019)
- NIMH Director's Group Award; National Institute of Mental Health (2017)
- NIMH Director's Group Award; National Institute of Mental Health (2016)
- NIMH Director's Group Award; National Institute of Mental Health (2014)
- Dean's Scholarship, Johns Hopkins Bloomberg School of Public Health (2012)
- Team Impact Award; Dana-Farber Cancer Institute (2010)
- Maryland Governor's Citation in recognition of "demonstration of high integrity and ability, meriting our great trust and respect" (2003)
- Barnes Award for Excellence in Character; Gonzaga College High School (2001)

SKILLS & KNOWLEDGE

- Human Subject Protection Training (CITI, NIH)
- Good Clinical Practice Training (NIH/OBSSR, CITI, NIDA, NIAID)
- Site Visit Consultant to HHS/OHRP (2014-Present)
- Analytical Problem Solving
- Project Management
- Personnel Management
- Employee and Schedule Management
- Computer Proficiencies: STATA, Tableau, Microsoft Office, Corel Office Suite, Adobe Acrobat Professional
- Intermediate level French and Italian
- Background Investigation Level 5b (MBI): Person of Public Trust (Confidential)
- Excellent written and oral communication skills
- Preparing presentations and written reports to communicate public health, scientific, and technical subjects to lay audiences

PUBLICATION

Kane, E. I. 3rd., & Gallo, J. J. (2017). Perspectives of IRB chairs on the informed consent process. *AJOB Empirical Bioethics*, 8(2), 137-143. doi: 10.1080/23294515.2016.1253628. PMID: 28949842